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Sedation in Acute Brain Injury: Less is More?

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Over the past decades, landmark interventional studies in general intensive1!care unit (ICU) patients have taught us that efforts to reduce the use of sedatives, by daily interruption (Kress et al. 2000; Girard et al. 2008), by not using sedatives as standard practice (Strøm et al. 2010), or by tapering sedatives to an awake but comfortable state (Mehta et al. 2012), lead to improvements in outcomes. Minimising sedation reduces the duration of mechanical ventilation, reduces ICU and hospital length of stay, facilitates early mobilisation and reduces healthcare cost. Additional advantages include a reduced incidence of brain dysfunction (coma or delirium), and a reduction in the need to perform technical examinations (such as CT, MRI or EEG) to assess unexplained changes in mental status. Most ICUs have implemented these insights in their clinical practice. Tapering sedatives might already be beneficial in the early phase after ICU admission, as the early sedation depth already independently predicts delayed extubation and increased mortality (Shehabi et al. 2012).

Unfortunately, most of these studies have not included acute brain injury patients, and specific large randomised clinical trials in the neuro-ICU population are lacking. On the one hand, neurocritical care physicians prefer to avoid unnecessary sedative drugs as much as possible, as they interfere with the neurological evaluation of the patients. An expert panel on the neurological examination of critically ill patients strongly recommends to daily interrupt or to reduce sedation in mechanically ventilated patients, in order to enhance neurological examination and improve short- and long-term outcomes, but advocates against this approach in patients with intracranial hypertension (Sharshar et al. 2014). On the other hand, sedatives are often prescribed in the neuro-ICU, sometimes in a continuous way, to control agitation, to reduce cerebral metabolism, to treat refractory seizures, to treat or prevent intracranial hypertension, to allow for mechanical ventilation to control $PaCO_2$ to facilitate temperature management or to control paroxysmal sympathetic hyperactivity. This widespread use, however, is not supported by evidence from randomised clinical trials. In the absence of such trials, it is important to understand how sedatives can possibly have a major impact on the outcomes of patients.

Current Sedation Practices in the Neuro-ICU

The fact that sedatives are frequently used in the neuro-ICU is demonstrated in several posthoc analyses from clinical trials or surveys: 77 to 90% of patients were under sedation in the first days of ICU stay after traumatic brain injury (TBI) (Hukkelhoven et al. 2002; Beretta et al. 2011). A recent survey of sedation practices in all 16 Scandinavian neurocritical care centres, over a ten-year period from 1999 to 2009 (Skoglund et al. 2013), demonstrated that over this decade, sedation practice had not changed much, and only half of the centres performed daily wake-up tests.

Daily Wake-Up Test and Analgo- Sedative Protocols in Practice

To date, the role of the daily wake-up test in the neuro-ICU is unclear. Only three small observational clinical studies have looked at the effect of the wake-up test on monitored parameters in acute brain injury patients (Skoglund et al. 2009; Helbok et al. 2012; Skoglund et al. 2014). Although, on average, the daily wake-up test appeared safe, with only a small increase in intracranial pressure (ICP) in the majority of patients, several patients after subarachnoid haemorrhage (SAH) and TBI developed potentially dangerous episodes of intracranial hypertension with reduced cerebral perfusion pressure (CPP) (Skoglund et al. 2009). In selected TBI patients these episodes occurred to a lesser extent and without changes in more advanced neuromonitoring parameters such as microdialysis, jugular bulb saturation and brain tissue oxygenation (Skoglund et al. 2014). In a prospective study conducted in 82 patients with various causes of acute brain injury (Helbok et al. 2012), one-third of the wake-up tests had to be aborted because of important side effects including ICP crises (>20 mmHg), agitation or systemic desaturation. This study also looked at the potential benefit of the wake-up test to detect a new neurological deficit, and found that this was the case in only one patient. All three studies were underpowered to study clinical outcome, and it is impossible to perform a benefit/risk analysis based on these small trials.

Reducing the amount of sedation can also be obtained through analgo-sedative protocols. An example of such a protocol for the neuro-ICU has been proposed, where analgesics (remifentanil for short-term use and fentanyl for longterm use) are to be used as first-line agents, followed by sedatives titrated to sedative scores (first propofol, supplemental midazolam as needed and barbiturates for refractory intracranial hypertension) (Egerod et al. 2010). In a before-after implementation study, this approach led to more pain-free patients, a reduced use of propofol and midazolam, an increase in remifentanil and fentanyl use and a faster awakening of patients without an increase in the duration of sedation or in the incidence of unplanned extubation.

Choice of Sedative

The ideal sedative in the neuro-ICU reduces the metabolism of the brain (CMRO2) while maintaining the coupling between cerebral blood flow (CBF) and CMRO2, does not augment ICP, maintains CPP, has no effect on cerebrovascular autoregulation, is anti-epileptic, short-acting and predictable (Albanèse et al. 2004). Unfortunately, such an ideal sedative does not appear to exist.

Synthetic opioids only have a minor effect on ICP and mean arterial pressure (MAP), although after induction a small and short increase in ICP and a decrease in MAP can be observed (Albanèse et al. 1999). Remifentanil has the advantage of being short-acting with predictable kinetics, and therefore could be first choice in those patients where early clinical assessment is important.

The most frequently used sedatives in the neuro-ICU are propofol and midazolam. The properties and drawbacks of both medications are well known. Propofol is rapid-acting, predictable and reliable, with fast awakening even after prolonged infusions. It reduces brain metabolism, with an associated reduction in CBF and ICP, and acts as an anticonvulsant. Propofol has important haemodynamic side effects. Particularly in the neuro-ICU, there are concerns about propofol infusion syndrome, and hence the dose and duration of propofol should be limited. Of the benzodiazepines, midazolam is the most frequently used. Midazolam has only minor haemodynamic-depressing effects, and reduces brain metabolism, CBF and ICP (albeit with a smaller effect than propofol). As with all benzodiazepines, midazolam is an anticonvulsive drug. After a prolonged infusion, the pharmacokinetics and thus the recovery become highly unpredictable, which is a major drawback in the neuro-ICU setting. In addition, benzodiazepine administration is an important and potentially modifiable risk factor for the development of ICU delirium (Pandharipande et al. 2006). A recent meta-analysis of 13 small randomised clinical trials, encompassing in total 380 TBI patients (Roberts et al. 2011) could not demonstrate convincing evidence that one sedative agent would be more efficacious than another. The authors concluded: “Insufficient data exist regarding the effects of sedative agents on neurologic outcome or mortality.”

The N-methyl-d-aspartate (NMDA) receptor antagonist ketamine has long been banned in brain-injured patients, following earlier claims that it could possibly increase the ICP. However, several prospective observational and interventional trials have been able to demonstrate that these claims are false. In fact, in patients after TBI,

ketamine either did not influence ICP (Bourgoin et al. 2005), resulted in a small but clinically insignificant increase in ICP accompanied with an increased CPP (Kolenda et al. 1996) or even significantly decreased ICP (Albanèse et al. 1997; Bar- Joseph et al, 2009).

Dexmedetomidine is a sedation agent targeting alpha-2 adrenergic receptors located in the locus coeruleus nucleus of the brainstem. It is approved for mild sedation. The main side effects of dexmedetomidine are hypotension and bradycardia. In a general ICU population dexmedetomidine provides a safe and effective sedation for patients who are less deeply sedated and thus more cooperative. At the same time dexmedetomidine reduces the incidence and duration of ICU delirium, as compared to propofol or benzodiazepines. In the neuro- ICU, only few data on its clinical use currently exist. A couple of small observational trials in neurosurgical patients indicate adequate sedation, with either no impact on or a reduction of ICP, although there are some concerns regarding hypotensive episodes (Aryan et al. 2006; James et al. 2012).

Sedatives and Neuroregeneration/ Neuroprotection

In critical brain-injured states sedatives are often given in order to reduce the metabolism of the brain, with the purpose of creating the optimal circumstances for the brain to recover. It is unclear whether sedatives possess specific neuroprotective properties with an impact on the outcome in these patients. Animal studies in experimental TBI in rats have indicated that midazolam as well as propofol have a negative impact on neuroregeneration and neurocognitive outcomes (Hertle et al. 2013; Thal et al. 2014). It is clear that these results cannot be extrapolated to the human TBI setting, but these studies suggest that the impact of sedatives on outcome is not necessarily positive, and that further research is needed to further explore these findings.

Cortical spreading depressions (CSD) are depolarisation waves that propagate across the grey matter of the brain at low velocity, and are associated with perturbations of the brain ion homeostasis and the efflux of excitatory amino acids. It is hypothesised that CSD might contribute to secondary brain injury after SAH or TBI. In a small nonrandomised study, ketamine was effective in stopping CSD (Sakowitz et al. 2009). A more recent retrospective study demonstrated that, of all sedatives, only the administration of ketamine was independently associated with a reduction of CSD, and that midazolam anaesthesia was even associated with an increased incidence of CSD (Hertle et al. 2012). The hypothesis that blocking CSD through NMDA antagonists could improve the outcome in brain-injured patients will be further examined in ongoing studies.

Conclusion

The use of sedatives in the neuro-ICU remains a dramatically underresearched field. In spite of that, sedatives are still frequently used in a continuous way. Attempts to reduce sedation through analgo-sedative protocols appears to be promising, but there are concerns about the risk versus benefit of daily sedative stops. Propofol and midazolam are still the most frequently used sedatives. There is a potential role for ketamine and dexmedetomidine in brain-injured patients. The specific effects of the different sedatives on neuroprotection or neuroregeneration warrant further research.

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