Critical care neurology

Five new things

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Summary

Critical care neurology has generated interest both because of the urgency to understand acute brain injury and because acute interventions could improve outcomes. Unifying themes include intervention without delay and early recognition of the potential for deterioration of the patient. While monitoring devices offer useful prognostic indicators, conducting a thorough clinical neurologic examination is paramount in determining the most effective course of patient management. Recent progress has been made in acute brain injury monitoring, more effective reversal of anticoagulation after cerebral hemorrhage, use of hypothermia as a therapeutic intervention, and in the management of severe Guillain-Barré syndrome.

Until now, observational studies (and occasional randomized trials) have framed the care of critically ill neurologic patients.

Here we briefly discuss five new things in the field of critical care neurology. These advances are pertinent not only to neurointensivists, but also to the practice of general neurologists who are often summoned to help manage these critically ill patients.

Monitoring acute brain injury

A frustrating issue in the care of an acutely injured neurologic patient is the lack of a reliable device or probe that can monitor brain dysfunction continuously. Real-time assessment of global or regional brain dysfunction could help clinicians recognize early worsening, prompt specific management changes, and monitor response to therapy. Certain parameters also could be used as surrogate endpoints in clinical trials. These devices are most useful in sedated and paralyzed patients when neurologic examination is limited to the assessment of pupillary reflexes. In all other cases, the findings from any monitoring device should be deemed a complement to a detailed and comprehensive clinical neurologic examination. Cerebral monitoring devices can provide a wealth of physiologic information, but it is unknown whether treatment guided by such information can improve clinical outcomes. Recent history has taught us that the use of even uniformly accepted devices may fail to improve—or may worsen—clinical outcome (i.e., the pulmonary artery catheter saga).

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Multimodality monitoring in the neurologic intensive care unit (ICU) can involve monitoring of increased intracranial pressure (ICP), microdialysis, brain tissue oxygenation, near infrared spectroscopy, and digital EEG with quantitative analysis or electrocorticography, often all at the same time. Crucial questions remain whether the monitored events require an intervention and what should be the thresholds to intervene. Skeptics are wary of the benefits of monitoring and caution against information overload. Proponents see a new creative way to monitor the brain and the potential for opening a large door.

Continuous EEG monitoring in the ICU is potentially useful,¹ but it is an expensive and labor-intensive program that requires expertise for interpretation. In many comatose patients both convulsive and nonconvulsive seizures are not clinically recognized. EEG may have a role in the detection of cerebral ischemia after subarachnoid hemorrhage and also may help detect episodes of cortical spreading depression that can affect the control of ICP or blood pressure.

A crucial question is whether the EEG findings—besides the obvious seizure activity—may have clinical relevance and whether they may alert to a developing secondary brain injury. In one study in traumatic brain injury continued EEG monitoring affected clinical decisions and may have reduced length of stay.² Another study identified electrographic seizures in a third of the patients with CNS infections.³ These observations are important, but not yet game-changing.

A major study has been recently published using microdialysis in 223 patients after traumatic brain injury.⁴ The University of Cambridge Group has been active in determining criteria for monitoring in patients with traumatic brain injury, and in this work they present the results of changes in microdialysis markers that include glucose, lactate, pyruvate, glutamate, glycerol, and the lactate/pyruvate ratio. Temporal patterns of abnormal lactate/pyruvate ratios were associated with increased mortality and unfavorable outcome independently of ICP, Glasgow Coma Scale score, or age. The study did not report a correlation with neurologic examination other than the Glasgow Coma Scale and presented no information on interventions that could change the abnormal neuronal biochemistry. The main question remains whether these findings on microdialysis represent an early indication of irreversible brain damage or provide an opportunity for timely treatment that could reverse the physiologic disturbance before irreparable structural damage occurs.

These and other techniques hold promise and need to be studied carefully in separate cohorts of patients. We know that findings from various monitoring modalities can refine our prognosis, but we still need to determine if they can guide therapy to improve clinical outcome. Novel noninvasive devices will likely become available in the near future. None of the current methods have been hailed as the Holy Grail of brain monitoring and none have redefined it. That would likely require a new original approach.

Hypothermia in acute brain injury

Induced hypothermia—also by many implicitly designated as therapeutic hypothermia—has become standard for the treatment of postresuscitation (anoxic-ischemic) encephalopathy. There is sufficient evidence that targeted temperature management has improved outcome in

some patients who remain comatose following cardiopulmonary resuscitation, particularly in survivors after ventricular fibrillation or pulseless ventricular tachycardia.

A recent large cohort of therapeutic hypothermia in 1,145 patients with out-of-hospital arrest from multiple hospitals in Paris confirmed better neurologic outcome in patients with shockable rhythms, but not in patients with nonshockable rhythms (asystole and pulseless electrical activity). Even a trend toward worse outcome was noted in this subset of patients. The lack of efficacy of therapeutic hypothermia in nonshockable rhythms may be explained by a prolonged and more complex resuscitation in these patients.⁵

Most cooling techniques employ cooling devices and cooling pads with embedded circulating water tubes. Shivering is suppressed with sedation and paralytic agents. Hypothermia (32–34°C) is maintained for 24 hours followed by device-controlled rewarming of 0.5°C per hour. In the largest European study, favorable outcome was found in 55% of the hypothermia group and 39% of the control group. Many hospitals throughout the world have therapeutic hypothermia protocols, but utilization is far from perfect.^{5,6} Overall, early on therapeutic hypothermia is applied to as few as 40% of all patients with out-of-hospital arrest even in hospitals with existing protocols. Several studies have shown a steep learning curve with utilization in up to 85% of patients with shockable rhythms.⁵

The only evidence-based indication of therapeutic hypothermia is in comatose survivors of cardiac arrest. It may have a similar benefit in near drowning victims and in patients with refractory status epilepticus, but these indications first require systemic studies. Trials using therapeutic hypothermia in traumatic brain injury found no difference in outcome, but the effect of rapid cooling and its specific use for patients with diffuse axonal injury and massive swelling remains to be studied. There is interest in the application of therapeutic hypothermia in stroke with ongoing prospective clinical trials, but there is so far no conclusive clinical evidence that hypothermia can improve the outcome of patients with stroke.

Therapeutic hypothermia may require considerable amounts of sedation and neuromuscular blockers and analgesics. Neurologic examination is markedly confounded by these agents, particularly if there is associated liver or renal injury due to resuscitation. Pharmacokinetics are profoundly changed in patients who have been subjected to therapeutic hypothermia and the effects of drugs may linger for days. How much this influences neurologic examination and

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prognostication is unresolved, but neurologists should be keenly alert to this pitfall. The common practice of using benzodiazepines, analgesics, and neuromuscular blocking agents creates a situation in which it is difficult to assess the patient reliably and neurologists should assure themselves that no lingering drugs are present. The prognostications of neurologic outcome after therapeutic hypothermia have not been defined reliably and there are conflicting results. Most studies have now questioned the reliability of an increase in neuron-specific enolase for prognostication after therapeutic hypothermia, but we suspect no neurologist would a priori rely on a single blood test to make important judgments on outcome. Rewarming may also be associated with re-emergence of electrographic seizures. Another unresolved issue is whether continuous EEG monitoring of comatose patients treated with therapeutic hypothermia could identify treatable seizures.

Emergency reversal of anticoagulation in cerebral hemorrhage

Treatment of cerebral hemorrhage initially is mostly supportive and includes blood pressure control and reversal of coagulation abnormalities if present. Expansion of the hematoma is common in the first hours and limiting this unwanted progression remains a major focus. Little progress has been made with clot stabilizers in patients with spontaneous cerebral hemorrhage, but such intervention is urgent in patients on anticoagulants. Aggressive reversal of warfarin effect is warranted when the international normalized ratio (INR) is greater than 1.4 (normal range is 0.9–1.3). Typically, reversal involves the use of fresh-frozen plasma and IV vitamin K, but more recent studies have suggested that recombinant factor VIIa or prothrombin complex concentrates (PCC) could be more helpful in reversing this condition.⁷ It is a well-accepted fact that fresh-frozen plasma and vitamin K alone may take many hours to reverse the effects of warfarin. The benefits of PCC over other treatments are as follows: a shorter time to normalize INR (less than 30 minutes), little volume of infusion, and administration of all vitamin K-dependent coagulation factors. Another compelling argument to use PCC is that it lasts longer than rFVIIa and less additional FFP may be needed (current guidelines in the management of cerebral hemorrhage have preferred the use of PCC over recombinant factor VIIa also because of generally more favorable costs, but the treatment is still expensive). PCC formulations without activated factors may be preferable because of a lower risk of thrombotic complications, although this theoretical advantage remains to be confirmed.

A related issue is whether platelet infusion should be administered to patients who had antiplatelet therapy prior to the cerebral hemorrhage. There is no evidence that platelet infusion reduces expansion of the hematoma or improves outcome. A considerable number of donor units may be needed to reverse the combined antiaggregant effect of aspirin and clopidogrel. One study in volunteers found 10 donor units for 300 mg and 15 donor units for 600 mg of clopidogrel were needed to completely reverse the platelet effects, thus suggesting a nonlinear therapeutic effect.⁸ Whether available platelet aggregation tests can reliably guide therapy in the emergency setting remains a matter of debate. A trial of platelet transfusion in cerebral hemorrhage associated with antiplatelet agents (PATCH) is ongoing.⁹

Last resort interventions to treat intracranial pressure after traumatic brain injury

The traditional approach to increased intracranial pressure has been CSF diversion, osmotic diuretics, hyperventilation, and more recently aggressive temperature control and even hypo-

thermia. Surgical management of refractory increased intracranial pressure is logical because it follows our understanding of the pressure–volume relationship of brain parenchyma within the skull. Reduction of mortality with lifting a large bone flap has been documented in multiple studies, demonstrating without a doubt that intracranial pressure is significantly decreased with decompression. Surgical technique of decompression after traumatic head injury involves bifrontoparietal decompression. Decompressive craniectomy is more commonly considered with penetrating injury and considered more or less essential to preempt the commonly encountered cerebral swelling. Complications associated with decompressive craniectomy after traumatic head injury and subsequent cranioplasty are subdural hygroma, relentless progression of contusions in up to 50%, and hydrocephalus in 25%. Intracranial infection is surprisingly low at less than 5%.

The neurosurgical and neurointensive care communities were therefore surprised to hear that a new randomized trial performed by Australian New Zealand Intensive Care Society Clinical Trial Group found that outcome was worse in patients treated with decompressive craniectomy.¹⁰ Patients were randomized when their intracranial pressure was greater than 20 mm Hg after first-tier therapies. Patients in the decompressive surgery group had worse extended Glasgow Outcome Scale scores. Nonetheless, the surgery did reduce intracranial pressure and resulted in shorter stay in the ICU. There was a beneficiary short-term effect, but worse long-term outcome. The trial has been criticized as being overly aggressive because the option to go into surgery only required increased intracranial pressure (more than 20 mm Hg) for more than 15 minutes and included intermittently increased intracranial pressures. Patients going into craniotomy had twice more often fixed pupils than the medical group and whether other brainstem reflexes were lost was not known. Another study—the Randomized Evaluation of Surgery with Craniectomy for Uncontrollable Elevation of intracranial pressure or RESCUE *icp* trial—is under way. In this trial, bilateral craniectomy is considered only after an ICP threshold of 25 mm Hg is reached for 1 to 2 hours.

Another treatment for refractory intracranial pressure is decompressive laparotomy, usually considered in polytrauma patients with abdominal compartment syndrome. Typically, abdominal compartment syndrome is seen in patients who have received high-volume fluid resuscitation. A dramatic effect in the control of ICP has been demonstrated in a number of cases.^{11,12}

Respiratory failure in Guillain-Barré syndrome

Judging the need for intubation in patients with Guillain-Barré syndrome (GBS) has remained difficult. Laboratory tests using forced maximal inspiratory and expiratory pressures and vital capacity may not be readily available and arterial blood gas measurements may be normal. Determining the prognostic reliability of clinical and laboratory factors is important because these elements are used to triage the admission to the ICU or the general ward and to decide which patients should be preemptively intubated.

Two recent studies addressed predictors of respiratory failure in GBS. One study included 34 ventilated patients in a series of 154 patients and found that vital capacity and the proxi-

Critical care neurology: Five new things

- *Methods of monitoring neuronal distress after a major brain insult are emerging, but the value of their clinical application is uncertain*
- *Prothrombin complex concentrates effectively reverse anticoagulation in warfarin-associated cerebral hemorrhage*
- *Decompressive craniectomy after nonpenetrating traumatic brain injury may control intracranial pressure but has no proven beneficial effect on outcome*
- *Induced hypothermia in comatose survivors after cardiac arrest is now commonly considered and may help certain patients*
- *Predictors of respiratory failure in Guillain-Barré syndrome have been recognized*

mal/distal compound muscle action potential ratio of the common peroneal nerve were independent predictors of mechanical ventilation (and also disability).¹³ Another study evaluated a cohort of 397 patients with GBS including 22% who needed mechanical ventilation. In this study, the main predictors of respiratory failure were time between onset of weakness and hospital admission, the presence of facial weakness or oropharyngeal dysfunction, and severity of limb weakness as assessed by the Medical Research Council sumscore.¹⁴ A scoring system to predict mechanical ventilation was developed, which incorporated these variables, and it was successfully validated in a separate set of patients. This respiratory insufficiency score is conspicuously devoid of markers of respiratory failure, but it shows that other clinical indicators may indirectly point toward the probability of respiratory failure. This study confirms the clinical impression that difficulty clearing secretions in a patient with a rapid onset (admitted 3 days after onset of weakness) and particularly severe GBS may herald or point toward diaphragmatic failure and eventually respiratory failure. Once the first week is passed intubation for neuromuscular respiratory failure becomes less probable.

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