

Update in Nonpulmonary Critical Care

Critical Care Neurology

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INTRODUCTION

There has been a dramatic change in the philosophy of treatment of patients who are critically ill with neurologic diseases. New therapies and monitoring techniques have shifted the focus of treatment from the reactive strategy that was the hallmark of both neurology and neurosurgery in the past, to an aggressive, preemptive strategy. In this review, we will focus on current controversies and recent advances.

NEUROMUSCULAR DISEASES

Fifteen to twenty percent of patients with myasthenia gravis will experience a myasthenia gravis exacerbation with impaired ventilation, called myasthenic crisis. The mortality of myasthenic crisis is 4% (1). The majority of patients die from medical complications and comorbid illnesses.

There are currently two opposing schools of thought on the issue of continuing or starting cholinesterase inhibitors in myasthenic crisis. Some practitioners advocate treating patients in myasthenic crisis with cholinesterase inhibitors in an effort to increase strength, and therefore, hopefully, decrease ventilator days. Conversely, some practitioners withhold cholinesterase inhibitors during the period of intubation. Pyridostigmine bromide (the most commonly used cholinesterase inhibitor) is metabolized by both cholinesterase and liver microsomal enzymes. In more severely ill patients, the half-life is variable and seems to be shorter than in less ill patients. This unpredictable metabolism raises concern that extubation will occur during the maximal effect of the cholinesterase inhibitors and that the patient may need to be reintubated during the drug nadir. There are no randomized, controlled trials comparing whether to start or continue cholinesterase inhibitor therapy.

Whereas immunosuppressive therapy for myasthenia gravis has been reserved for cases in which cholinesterase inhibitors do not adequately control symptoms, prednisone has been used routinely for myasthenic crisis both during the acute phase and after discharge. The long-term side effects of systemic steroid therapy are numerous. For instance, systemic corticosteroid therapy has been observed to transiently exacerbate the symptoms of myasthenic crisis in as many as 48% of patients, within the first 4 to 7 d of treatment. Although a retrospective analysis by Berrouschoot and colleagues (2) found no difference in outcome at 3 mo in patients treated with either cho-

linesterase inhibitors alone, plasma exchange, or systemic steroid therapy, in our current experience, steroids are believed to be beneficial. Clearly, better studies need to be done. Although clinical trials investigating the optimal dose of systemic steroids have not been done, a reasonable approach is to begin with 1 mg/kg of prednisone or equivalent, once daily.

Plasma exchange is effective in myasthenic crisis. The standard therapeutic course is five exchanges on alternate days. Studies of daily plasma exchange compared with every other day exchange have demonstrated no statistically significant improvement in strength or number of days of mechanical ventilation but have shown a trend toward improved strength at the end of therapy without increased side effects (3).

Since 1984, intravenous immunoglobulin (IVIg) therapy has also been used as therapy for myasthenic crisis (4). The standard course is 3 to 5 administrations of 0.4 g/kg. Significant side effects are less common than with plasma exchange. There is risk of hepatitis B and C as well as a theoretical risk of human immunodeficiency virus (HIV) exposure with IVIg.

There has been only one clinical trial comparing plasma exchange and IVIg (5). A randomized clinical trial done in 1997 failed to show a significant difference in outcome with either of the two therapies but did show increased side effects with plasma exchange (5). A retrospective analysis on the same topic showed the failure rate of one course of IVIg treatment was 20% (6). At this time, because of the high failure rate with one course of IVIg, unless contraindicated or unavailable, it is our opinion that plasma exchange in combination with systemic steroid therapy is the treatment of choice for myasthenic crisis.

New therapies are being studied for the treatment of severe myasthenia gravis. Both double-filtration plasmapheresis and immunoadsorption of plasma are techniques in which certain plasma components are returned to the patient. Two studies have shown the effectiveness and safety of the immunoadsorption but have not compared it with conventional plasma exchange (7). Okada and colleagues compared double-filtration plasmapheresis, and immunoadsorption with typical plasma exchange and found that there was no difference in outcome but a subjective improvement in patients' symptoms with the double-filtration plasmapheresis (8).

Respiratory failure in myasthenia gravis can come from ventilatory failure, or failure to protect the upper airway owing to bulbar muscle weakness, or both. A vital capacity below 15 ml/kg has been advocated as an indication for intubation. Signs that the patient is unable to protect the airway or is having upper airway collapse during inspiration may also necessitate intubation. Arterial blood gas and saturation monitoring are often not helpful in making the decision to intubate because hypercapnia is a late finding. Normal PaCO₂ and PaO₂ do not exclude the possibility of ventilatory failure requiring mechanical ventilation.

Guillain-Barré syndrome has been associated with cytomegalovirus, HIV, Epstein-Barr virus, and bacterial infections with *Campylobacter jejuni*. The majority of patients with Guil-

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Guillain-Barré syndrome have the demyelinating form as opposed to the axonal form. The prognosis for the demyelinating form is better than that for the axonal form.

Treatment of Guillain-Barré syndrome was largely supportive until the introduction of plasma exchange in 1978. In a review of the data, Raphael and colleagues (9) showed that for patients with mild disease, two plasmapheresis sessions were sufficient to gain maximal efficacy. In more severely affected patients, four sessions reached maximal efficacy. There was no additional efficacy with more sessions.

IVIg and typical plasma exchange have been shown to have similar efficacy (10). The complication risk was also similar. Combination of IVIg with plasma exchange showed no added benefit (11).

Patients with Guillain-Barré syndrome become critically ill when they develop ventilatory failure or autonomic insufficiency. Mortality from this syndrome is due most often to complications from mechanical ventilation but can also occur as a result of sudden cardiac death from autonomic failure. Patients can experience hypotension, tachycardia, bradycardia, and constipation. Most often the symptoms are mild and resolve as the recovery phase of the disease begins.

A vital capacity below 15 ml/kg has been advocated as an indication to electively intubate and mechanically ventilate the patient. Because Guillain-Barré syndrome is a monophasic illness, cessation of mechanical ventilation is less difficult a decision than with myasthenic crisis.

CONVULSIVE STATUS EPILEPTICUS

Convulsive status epilepticus is a common neurologic disease. There has been little agreement on what duration of seizure constitutes convulsive status epilepticus. The historical definition is 30 continuous minutes of convulsions or more than one seizure without a clear interictal period. This definition is based on microscopic evidence of neuronal injury in animal models, not on human outcome data. Lowenstein and coworkers have proposed that 5 min of continuous seizure activity or successive seizures without clearing of the sensorium replace the historical definition (12).

In the last 3 yr, there have been a number of new medications that have become available to treat epilepsy. Although there are no current studies to support their routine use, three of these new antiepileptic formulations, intrarectal diazepam, intravenous valproate, and fosphenytoin, have the potential to be used in the treatment of status epilepticus in adults. Fosphenytoin, a prodrug of phenytoin, is currently being used in many centers as a substitute for phenytoin in the treatment of status epilepticus. Its use decreases the incidence of hypotension that is associated with rapid administration of phenytoin.

The remaining small number of available intravenous, antiepileptic medications has limited the treatment of convulsive status epilepticus. A commonly used algorithm for treatment includes a small dose of a benzodiazepine followed by either phenytoin or phenobarbital. A recent study by Treiman and associates compared high-dose lorazepam, standard dosing of phenytoin, phenobarbital, and combined phenytoin and lorazepam (13). In this study, 0.1 mg/kg body weight of lorazepam alone is just as effective as the other combinations at stopping electrographic seizure activity within 20 min and inhibited repeat seizure activity for 24 h.

The treatment of convulsive status epilepticus refractory to first-line treatment has changed over the last decade. Pentobarbital was used almost exclusively until the introduction of midazolam and propofol. Midazolam has been shown to successfully stop status epilepticus in adults (14). Propofol was

initially thought to be a proconvulsant, but recent data show that it is an effective treatment if used in high doses (15). There is a limited amount of data on the efficacy of ketamine in status epilepticus. There is no current consensus and no prospective data comparing the four medicines.

Electroencephalography (EEG) monitoring is essential in the treatment of status epilepticus. In a study done by DeLorenzo and colleagues, after cessation of convulsions, 48% of patients continued to have seizure activity and 14% of patients had persistent nonconvulsive status epilepticus (16). Continuous EEG monitoring should be started as soon as possible after the initiation of pharmacologic therapy of status epilepticus.

Nonconvulsive status epilepticus has recently been found in 8% of patients hospitalized in a coma (17). The treatment of nonconvulsive status epilepticus not in the setting of previous convulsive epilepticus is controversial. Unlike convulsive status epilepticus, there is no light microscopic evidence of neuronal injury after a set period of nonconvulsive status epilepticus. In addition, there are less data concerning outcome of nonconvulsive status epilepticus. Although most neurologists believe nonconvulsive status epilepticus should be treated, there are differing opinions as to whether it should be treated as an emergency and whether pentobarbital, propofol, or midazolam are warranted. Our recommendation, pending definitive studies, is to treat nonconvulsive status epilepticus aggressively, just as one would convulsive status epilepticus.

BRAIN TRAUMA AND INCREASED INTRACRANIAL PRESSURE

Initially, the aim of treatment of increased intracranial pressure is to attempt to reverse the underlying cause of the edema. By the time cerebral edema has reached the point of herniation, the cause of the edema becomes less important and common treatment modalities are employed. Volume reduction, hyperventilation, hyperosmolar state, barbiturates, and hypothermia are the most commonly employed.

Corticosteroid therapy was used a great deal in the 1970s and 1980s, but it has fallen out of favor in the past 10 yr. Corticosteroids are beneficial in cerebral edema due to neoplasm but have not improved outcome of increased intracranial pressure in other disease states (18).

Hyperventilation decreases intracranial pressure by causing respiratory alkalosis, which constricts arterioles. It is important to note that damaged areas of the brain lose the ability to autoregulate and do not reliably vasoconstrict (19). Prolonged, prophylactic hyperventilation may worsen outcome from traumatic brain injury by the putative mechanism of decreased brain tissue Pa_{O₂} (20). In current practice, hyperventilation is used only for transient increases of intracranial pressure as an acute temporizing measure. The Pa_{CO₂} level should be monitored and levels of Pa_{CO₂} should be decreased in increments of 5 mm Hg.

Mannitol causes rapid reversal of increased intracranial pressure signs and symptoms. When administered as 0.25 to 1 g/kg body weight dose, it can reverse the signs of herniation within minutes. Its function is in part due to an osmotic diuresis from the increased osmolarity of the blood but this is unlikely to be its only effect. It is effective for 16 to 48 h after which the brain accommodates to the new osmolarity. It can be given repeatedly in boluses or administered slowly as an intravenous infusion.

Barbiturates and moderate hypothermia decrease cerebral metabolism and therefore may decrease the effects of anoxia in neurons. Decompressive surgery has also been studied for head injury (21). The data are inconclusive but may favor

early decompression in head injury in the future. Current studies looking at the use of decompressive surgery in stroke, but not head injury, in a randomized manner are ongoing but not yet available.

STROKE

The most commonly used diagnostic test to detect acute stroke is computed tomography (CT) scans of the head. The wide availability of this technique across the world has made this a mandatory test to perform in a patient with acute loss of neurologic function. A CT scan is used initially to rule out intracerebral hemorrhage (22).

Magnetic resonance imaging (MRI) has proved to be more sensitive for acute stroke. Conventional sequences such as proton-density weighted images can detect stroke much earlier than can CT scan. Newer modalities such as fluid-attenuated inversion recovery sequences (FLAIR), diffusion-weighted sequences, and perfusion sequences are able to reliably detect stroke in evolution. These modalities will likely, in the future, supplant CT scans as the test of choice for the diagnosis of acute stroke (22).

Treatment of stroke includes clot lysis if possible, prevention of secondary stroke extension, and prevention of recurrent stroke. Recombinant tissue plasminogen activator (rt-PA) administered intravenously within 180 min of the onset of symptoms is effective in improving long-term outcome (23). The use of rt-PA in the National Institute of Neurological Disorders and Stroke (NINDS) study shows an 11% increase in the number of patients with little or no disability compared with placebo. The use of rt-PA does increase the risk of intracerebral bleeding but the overall mortality is unchanged (23). Unlike cardiac thrombolysis with rt-PA, concomitant heparin is not used for stroke therapy.

A study addressing site-directed, intra-arterial prothrombinolytic showed a significant increase in recanalization of the thrombosed artery ($p < 0.001$) and showed a smaller but still significant benefit in the primary endpoint ($p = 0.04$) (24). Further studies are needed to evaluate the use of site-directed thrombolysis in the 180- to 360-min window.

The role of heparin therapy after acute stroke is unclear. There are now data that suggest there is no increased risk of bleeding with heparin in patients with suspected embolic stroke (25). Many practitioners use heparin in all patients who are suspected to have embolic disease until the workup is completed. Recently, a randomized controlled trial showed no benefit to giving low-molecular-weight heparin to all stroke patients in the acute setting (26). Many neurologists believe that there is a role for unfractionated heparin in posterior circulation stroke but definitive studies are lacking.

Transthoracic and transesophageal echocardiography, the most commonly employed tests to look for cardioembolic sources, are useful in patients with cardiac history or arrhythmia but offer little benefit in the absence of electrocardiogram abnormalities or a clear history of atrial fibrillation (27). In those patients with embolic sources, anticoagulation is continued indefinitely.

The current recommendation for post-stroke management is to allow systemic blood pressure to remain supranormal unless the systolic blood pressure is greater than 200 mm Hg, the diastolic blood pressure is greater than 100 mm Hg, or the patient shows signs of malignant hypertension. Blood glucose elevation at the time of admission to the hospital is associated with poorer prognosis (28). There is consensus that after a stroke, intravenous fluids without dextrose are preferable and elevation of glucose above the normal range should be treated.

In a large case series, cerebral decompression by hemicraniectomy after large-territory, middle cerebral artery strokes has been shown to decrease mortality and increase functional outcome (29). Currently, a randomized, controlled trial is being done to determine which patients may benefit from this therapy.

Intracerebral hemorrhage (ICH) accounts for 15% of all strokes. Surgical evacuation of clot in the brain has fallen out of favor in the last 20 yr. Recently, a new interest in surgical evaluation with a goal of early surgery has surfaced. Many older trials showed no significant difference in outcome between surgically treated patients and medically treated patients (30). Recently, Zuccarello and colleagues showed a trend toward improved outcome if surgery was performed within 24 h of the onset of symptoms (31). A multicenter trial investigating surgery within 24 h should shed some light on whether this therapy is effective. For patients with cerebellar hemorrhage, early decompressive craniotomy has been shown to be an important intervention (30). Stereotactic surgical techniques may prove to be effective and safer for evacuation of hemorrhages.

Medical management is aimed at prevention of secondary injury. There are no randomized studies to guide therapy so most recommendations are made by consensus. Most practitioners control systolic blood pressure below 160 mm Hg for the first 24 to 48 h. Normal volume status is considered optimal in these situations; there is no benefit to hypovolemia or hypervolemia. Patients with hemorrhages that extend or compress cortical structures predispose the patient to seizures; therefore, anticonvulsant therapy with phenytoin is often used. Corticosteroid therapy is of no benefit in intracerebral hemorrhage and may increase the number of infections (32).

SUBARACHNOID HEMORRHAGE

The initial treatment of subarachnoid hemorrhage is aimed at prevention of secondary injury and preparation for surgical or endovascular intervention. The most common causes of secondary injury are rebleeding, vasospasm, seizure, volume and osmolar disturbances, and cardiovascular complications.

Cerebral vasospasm is a reaction in the cerebral blood vessels to aneurysmal subarachnoid bleeding that usually occurs 4 to 14 d after bleeding. Prophylaxis with nimodipine, a calcium channel blocker, has been shown to improve outcome (33). A sister compound, nicardipine, improves radiographic vasospasm but has not been shown to improve mortality (34). Hypertensive, hypervolemic, hemodilutional therapy (HHT) is a commonly used method of increasing flow across the vasospastic area. There are observational data but no controlled trials that suggest that HHT improves outcome for patients with vasospasm (35). Angiographic manipulation of vasospastic vessels with angioplasty and papaverine injection has short-lived effects but, in our experience, can be useful.

Seizures occur in more than 6% of patients with subarachnoid hemorrhage with the majority occurring at the time of bleeding. Prophylaxis with phenytoin (15 to 20 mg/kg body weight) is practiced in many centers.

Hyponatremia is a common subacute complication after a subarachnoid hemorrhage. Most often, hyponatremia is caused by cerebral salt wasting syndrome that is mediated by release of atrial or brain-derived natriuretic factor. Because hypovolemia appears to worsen outcome in subarachnoid hemorrhage, wasting of sodium is treated with hypertonic saline infusions (36).

SPINAL CORD TRAUMA

In acute spinal cord injury, the level of the injury and the severity of the spinal cord trauma are the most important indica-

tors of prognosis. The majority of critical care issues occur for patients with cervical spine injuries. The most common secondary complications are respiratory failure from loss of intercostal and phrenic innervation and loss of sympathetic tone.

Corticosteroids in high doses (methylprednisolone 30 mg/kg bolus followed by infusion of 5.4 mg/kg/h) have been shown to make a small but measurable improvement in outcome if administered within 8 h of the injury. A recent study showed that those patients who present in the first 3 h benefited from only 24 h of therapy whereas those who presented from 3 h to 8 h benefitted more from 48 h of therapy (37).

Respiratory failure is more likely to be permanent with higher cervical injuries that affect the phrenic nerve and therefore, the diaphragm. Even in those who do not have diaphragmatic dysfunction, respiratory failure can occur presumably because of loss of the muscular tone in the thorax that increases the compliance of the chest.

Autonomic insufficiency occurs in injuries above the thoracic spinal levels. Injuries below the thoracic spine are less likely to cause profound hypotension, but can cause some drop in blood pressure owing to pooling of blood in parietic limbs. The therapy for this decrease in blood pressure is to administer fluids and pressors, usually dopamine. Binding of the lower extremities prevents pooling especially when the patient is not recumbent. Over time, this dependence on external pressors diminishes and most patients regulate their own blood pressure over time. During times of stress such as infections, blood pressure lability may return.

Early physical therapy and good respiratory care are important to prevent the most common complications, deep vein thrombosis/pulmonary embolism, and pneumonia. Unfractionated heparin and compression stockings have been shown to decrease the incidence of deep vein thrombosis (38). Pneumonia is commonly the result of impaired cough response. "Quad coughing" is an effective way of clearing secretions but may cause trauma if a Greenfield filter has been placed for deep vein thrombosis. Often, patients require tracheostomy for suctioning.

Conclusion

Although research into neurologic conditions in critical care has recently improved our knowledge of the pathophysiology and treatment of these diseases, a great deal remains to be done. Many commonly used treatments have not been tested in rigorous experimental studies. It is likely that in the next 5 to 10 yr some of the treatments mentioned in this report will be replaced by newer, more effective therapies.

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