Recognition and Management of Intracranial Hypertension

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Intracranial hypertension, that is, the sustained elevation of pressure within the cranium, can be the result of a primary central nervous system process, or a secondary complication of a concurrent systemic illness. Independent of the underlying etiology, unremitting elevation of intracranial pressure (ICP) represents an absolute emergency that not infrequently results in disabling and deadly consequences if left unattended. Advances in the understanding of the underlying pathophysiology and dynamics of ICP—provoking injury and recent progress in the treatment of severe, intractable ICP elevations allows the astute clinician to protect the brain from secondary injury and to improve outcome. Unfortunately, however, the management of intracranial hypertension is frequently approached in an overly simplistic manner, starting not only with the common denial and inexperience of physicians to detect and monitor raised ICP but also with the sequential application of various ICP lowering strategies in a cookbook-like fashion. In contrast, dedicated management of intracranial hypertension is best tailored to patient's individual situation and to the continuous changes in response to neuromedical and neurosurgical therapeutic maneuvers. This overview will review both the basic and advanced principles that should be considered when arriving at an individualized strategic management plan for a patient with brain swelling and/or intracranial hypertension.

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Cerebral Hemodynamic Considerations

Intracranial pressure and intracranial compliance

When it is monitored, the ICP tracing is a ballistic waveform similar to the systemic arterial pressure curve (Fig. 1): it has a narrow “pulse pressure” and is expressed, by convention, as its mean measured in millimeter of mercury (mmHg). The normal mean ICP is generally between 5–10 mmHg, and it fluctuates to higher levels depending on physiological factors such as Valsalva maneuver and body position. The ICP wave contains three consecutive peaks in descending order, Peak 1 to 3 which are called percussion wave, tidal wave, and dicrotic wave, respectively. In addition, fluctuations in the baseline of the ICP waveform with breathing usually reflect a decrease in intracranial compliance, and it can occur and accentuate even before an elevation in the actual ICP value. This knowledge can be helpful in selected situations.

For example, when a patient has fulminant hepatic failure observation of these subtle changes in the ICP waveform can signal the evolution of brain swelling before it is clinically apparent or the ICP has increased.

In normal adults, the skull is a rigid container and contains brain parenchyma, fluid (interstitial and cerebrospinal), and blood (arterial and venous). In the average adult male the intracranial volumes approximate to 1,450 ml for the brain, 110 ml blood, and 65 ml of CSF. Expansion of any of these “compartments” or the addition of a space occupying process can lead to ICP elevation. The extent of the ICP elevation depends on many factors, most importantly the individual patient’s intracranial compliance, that is, the unit change of intracranial volume per unit change of intracranial pressure (ΔV/ΔP). A high compliance denotes a system that will accommodate significant changes in volume (i.e., by diverting blood and CSF out of the cranium) without little increases in pressure and vice versa, a reduced compliance is found when the addition of small volumes to the intracranial space induces marked changes in ICP. Compliance or more technically correct described as its inverse, the brain elastance (change of pressure per change of volume (ΔP/ΔV), can graphically be depicted in the intracranial

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pressure-volume curve (Fig. 2) where the initial part of the idealized curve represents the state of high compliance (= high elastance) and the more final graph segment denotes low compliance (= low elastance).

There is decreasing intracranial compliance as the intracranial fluid dynamic relationship shifts to the right along the intracranial pressure-volume curve. At the bedside, abnormalities in intracranial compliance are often readily realized by observing the ICP monitor and identifying an increase in peak 2 amplitude (often exceeding peak 1) and blunting of peak 3.

The concepts of the intracranial pressure-volume relationships and intracranial compliance can be applied clinically when evaluating brain imaging studies to estimate the likelihood of intracranial hypertension in a patient who suffers a space occupying intracranial process. For example, initial axial head computerized tomography (CT) scan of a patient with brain swelling from a middle cerebral artery territory infarction may still show compressible spaces around the swollen brain (e.g. basal cisterns, ipsilateral lateral ventricle, and ipsilateral cortical sulci) and it is reasonable to expect that the ICP is not yet importantly or persistently elevated.

Cerebral blood flow and cerebral perfusion pressure

Alterations in cerebral blood flow (CBF), both too much or too little, can disturb the brain homeostatic mechanisms and further aggravate cerebral injury. Regulation of arterial blood flow is accomplished by constant regulation of the caliber of arterioles and arterial luminal diameter. Among others, in response to changes in both mean arterial pressure and partial pressures of oxygen (pO2) and carbon dioxide (pCO2). At fixed arterial pressures, CBF changes linearly at a pCO2 range from 20 to 80 mmHg. Such CBF changes translate directly into changes of cerebral blood volume (CBV) accomplishing an approximately 5 cc CBV reduction in an averaged sized brain for every -10 mmHg pCO2 reduction. In contrast, CBF and hence CBV remain constant at physiologic variations of pO2; however, pO2 levels of <50 mmHg induce brisk brain hyperemia by increasing CBV. At fixed gas pressures, on the other hand, CBF and CBV are held constant throughout a wide range (50 to 150 mmHg) of mean arterial pressures (MAP) by cerebral counter-regulatory vasodilatation and vasoconstriction. This autoregulation can not only be overwhelmed by MAP increases (i.e., malignant hypertension) and blood pressure failure (i.e., systemic arrest) but also in chronic hypertensive patients, the autoregulatory MAP thresholds are shifted to the right making the brain more vulnerable to low blood pressure values. Fig. 3 graphically depicts this relationship for normotensive
The concept of cerebral perfusion pressure (CPP) is an important clinical guide to management of the dynamic interplay between ICP and blood pressure. By definition, the CPP refers to the difference between the MAP and the cerebral venous pressure. Since the cerebral venous pressure is approximated by the ICP in most cases, the generally accepted CPP equation is:

\[
\text{CPP} = \text{MAP} - \text{ICP}
\]

This equation emphasizes the important point that the primary mechanism of cerebral injury from intracranial hypertension is cerebral ischemia from compromised cerebral perfusion. In normal individuals, cerebral perfusion is well-maintained with typical MAP values of 70 to 90 mmHg and ICPs of <15 mmHg. Notably, CBF is not a direct correlate of CPP, since autoregulation allows the CBF to remain constant in normotensive patients once the CPP exceeds approximately 40 mmHg in previously normotensive patients.

Importantly, the physiological relationship between blood pressure, CBF, and CPP are less predictable in damaged brain regions where autoregulation is impaired. In brain regions without intact autoregulation, relative blood pressure lowering or elevation, even within a normal range, can lead to regional cerebral ischemia or hyperemia, respectively. In most clinical scenarios, it is best to maintain CPP in the 60–80 mmHg range in euglycemic patients, but the target CPP must be adjusted based on the priorities dictated by each particular clinical situation. For example, when brain hyperemia is one of the causes of brain swelling, maintaining CPP at a lower level can be an important therapeutic strategy. On the other hand, maintaining CPP on the generous side can provide a useful margin of "reserve" when there are plateaus in ICP that can suddenly and unpredictably challenge brain perfusion.

Furthermore, higher CPP should be tolerated in circumstances when blood pressure augmentation is used in selected patients as a treatment strategy for raised ICP based on its ability to cause autoregulatory reflex vasoconstriction, reuced cerebral blood volume, and ICP lowering.

Plateau waves

One of the most feared and devastating complication of patients with intracranial hypertension and poor intracranial compliance are plateau waves (PW). PW are acute elevations in ICP, at times in the range of 50–100 mmHg in patients with reduced intracranial compliance. They can last from several minutes to more protracted durations in extreme cases. Resolution of a PW is often as abrupt as its occurrence. While there are many causes of PW, one common and important mechanism is generalized cerebral vasodilatation from an autoregulatory response to a decrement in systemic blood pressure. Other causes include processes that can cause an increase in CBF and/or cerebral blood volume. Independent of the underlying etiology, PW can be disabling or even deadly leading to brain herniation and cerebral perfusion arrest. Since compromised CPP can play a role in the occurrence in the most severe PW, relative blood pressure lowering should be avoided and/or rapidly treated. Similarly, during a PW, maneuvers that accentuate CPP such as blood pressure augmentation will abort the process in many circumstances. Even if blood pressure augmentation does not abort the process, it can prevent cerebral ischemia until other treatment modalities can successful lower the ICP.

Cerebral Edema, Mass Effect and Brain Tissue Displacement

Cerebral edema

Cerebral edema is defined as an increase in brain water content. The more classical categorization of cerebral edema by etiology differentiates that caused by cellular injury (cytotoxic edema) vs. breakdown of the blood brain barrier (hydrostatic or vasogenic edema). Hydrocephalic edema, ischemic edema (a combination of cytotoxic and vasogenic), osmotic edema, and hydrostatic edema have also been characterized as distinct entities by some authors based on their mechanisms and the location of the edema fluid. Vasogenic edema is comprised of a plasma derived protein rich exudates due to an alteration in the blood brain barrier. It occurs in both gray and white matter, but it tend to predom-
Brain Tissue Displacement and Herniation Syndromes

It is important to differentiate mass effect and brain tissue displacement (BTD) from intracranial hypertension. As should be apparent from intracranial pressure-volume curve in Fig. 1, there can be a substantial amount of mass effect without an important global elevation in ICP, and mass effect alone can cause brain damage through its regional effect on brain perfusion and/or brain tissue displacement (e.g. herniation). BTD is a distortion of brain anatomy, and depression of consciousness is one common, even though sometimes late, accompanying sign associate with brain distortion. Autonomic changes such as increasing blood pressure and exaggeration of the respiratory sinus arrhythmia are also changes that can be seen early with evolving BTD, and recognition of these signs can serve as an early warning of this life-threatening phenomenon. The consequences of BTD depends on the extent and duration of the process, and its occurrence alone should not deter attempts to reverse the process.

It is useful to note the relationship between horizontal brain displacement and depressed consciousness. With acute intracranial mass lesions, lateral and latero-caudal displacement of midline brain structures (diencephalon and upper brainstem) correlate with depression of consciousness. This can be practically quantified by measuring horizontal shift of the pineal gland on non-contrast CT scans. In the classical study describing this important relationship, horizontal shift of the pineal (from midline) by 0–3 mm correlated with alertness: 3–4 mm, with drowsiness: 6–8 mm, with stupor: and >8 mm, with coma. This has clinically applicability in determining the cause of depressed consciousness in individual patients. When the extent of horizontal shift does not readily explain a patient’s level of consciousness, other potential etiological factors must be considered.

As already mentioned, BTD from regional brain swelling can occur even without important ICP elevations, and it can have devastating consequences. For an example, an acute middle cranial fossa process such as an acute temporal hematoma can cause lateral transtentorial herniation without a profound rise in ICP. As a result, successful management of BTD (i.e., hematoma evacuation) requires strategic consideration of its significance in individual cases. This is particularly important since the treatment for elevated ICP is not necessarily the same as it is for BTD. In fact, ICP-directed medical treatments can, in certain cases accentuate BTD.

Intracranial Pressure Monitors

When a patient at high risk for brain swelling is encoun-
tered, a proactive approach to management should begin. This includes developing a monitoring strategy for early detection of the problem and planning the best management approach if it does occur. In at risk patients without important brain swelling, invasive ICP monitoring may not yet be appropriate. However, early insertion of an ICP monitor may be necessary if the risk of the problem is very high (e.g., fulminant hepatic failure), serial examination and/or imaging cannot be performed properly or readily (e.g., the intubated and/or heavily sedated patients), and/or the determination of the ICP will translate to important therapeutic changes.

It should be clear that the most rational and sophisticated management of intracranial hypertension should be based on continuous ICP and CPP monitoring. While active management of ICP guided by ICP monitoring has not shown a consistent benefit in outcome, it is difficult to study this well in humans for a variety of methodological reasons. Most experienced physicians appreciate that ICP monitoring is of value and benefit in properly selected patients. In particular, processes associated with life-threatening elevation of ICP, a rapidly expanding intracranial mass, or a disease in which ICP elevation is likely to be progressive demanding proactive preservation of CPP represent some generally accepted indications for monitor insertion.

ICP can be monitored from several intracranial sites (Fig. 4). The most commonly employed ICP monitoring devices are ventricular catheters and parenchymal monitors. Both can be readily placed at the bedside with a twist drill by neurosurgeons or experienced neurocritical care physicians. External ventricular catheters (EVD) have been considered the gold standard for ICP monitoring, based on their reliability and ability to drain CSF as an alternative for ICP control. It is the most invasive of alternatives, however, and EVD placement is associated with higher risks of infection, intracranial hemorrhage, and, in our experience, seizures.13,14 Furthermore, EVD are likely of no use patients with small, slit-like ventricles in which continuing CSF drainage and hence, pressure monitoring, is unrealistic.

Parenchymal monitors offer some advantages over other systems in that they allow rapid and safe placement with accurate measurements and less risk of infection. The presently available parenchymal monitors employ either fiberoptic or strain gauge technology. The tip of parenchymal monitors is placed several millimeters into the brain parenchyma through a twist drill whole placed over the convexity. Since the maximal ICP is in the region of an intracranial mass, they are best placed ipsilateral to a mass lesion unless it is deemed unsafe based on the suspected etiology of the process.

Parenchymal monitors are often placed through and secured by a bolt screwed into the cranium after the placement of a small hole with a twist drill: a more necessary step with the fiberoptic catheters that can break if bent. The monitors based on strain gauge technology can be bent and allow a wider flexibility of placement methods and configurations relative to the fiberoptic systems. However, both technologies are widely used and the selection of monitor type is often based on institutional history and the personal experience and preferences of those who insert them. While ventricular catheters are fluid coupled systems that can be zeroed by nurses at the bedside, parenchymal monitors are zeroed prior to insertion and can only be re-zeroed through removing and re-inserting them. The advantages of parenchymal monitors over ventricular catheters are, to some degree, counter-balanced by drift in the ICP readings over time and the inability to drain CSF for ICP control.15 While these various advantages and disadvantages are important considerations when selecting the ICP monitor type, the anatomy and physiology of the process requiring a monitor often dictates the best suited monitoring method.

As mentioned in earlier in this chapter, ICP elevation can be imperfectly predicted through analysis of brain imaging studies, usually CT. When the ICP from any monitor type is either much lower or higher than expected clinically and based on imaging analysis, steps should be taken to determine the accuracy of the monitor. At times this requires re-zeroing the monitor or replacement, at times in even in a new position or location. Blind trust of monitoring information that is significantly contrary to clinical expectations can lead to mismanagement and avoidable complications.

**FIGURE 4.** ICP can be monitored from several intracranial sites, the most commonly employed ICP monitoring devices are external ventricular catheters (on left) and parenchymal monitors (on right). Parenchymal monitors, employing either fiberoptic or strain gauge technology, offer some advantages over other systems in that they allow rapid and safe placement with accurate measurements and less risk of infection. Parenchymal monitors are inserted at the bedside with placing the sensor tip several millimeters into the brain parenchyma. Since the maximal ICP is in the region of an intracranial mass, they are best placed ipsilateral to a mass lesion unless it is deemed unsafe based on the suspected etiology of the process.
Management of Intracranial Pressure

Controlling aggravating factors

Patient positioning is an important aspect of the care of patients with intracranial hypertension. Lateral head rotation, rotating neck movements, and restrictive devices around the neck (e.g. endotracheal tube neck straps) can compromise jugular venous drainage. The head should be kept in the neutral forward position. Sometimes, towel rolls placed on both sides of the head can be useful in maintaining the neutral position. Head elevation lower ICP by enhancing CSF drainage and maximizing cerebral venous output. CSF and cerebral venous blood are maximally displaced with severe intracranial hypertension, challenging the benefits of head elevation in these patients. The logical approach is to individualize the ideal head and neck position based on clinical observation of the patient and ICP monitoring, when available. When ICP monitoring is not available, head elevations of 30–40 degrees allows the most consistent reduction in ICP.16

Fever should be treated aggressively because body temperature elevations increase ICP by increasing cerebral metabolism, cerebral blood flow, and cerebral edema.17,18 Acetaminophen should be administered (assuming normal hepatic function) along with a diligent search for treatable infection. There should be a low threshold for using empiric antibiotics for the most likely source, even though centrally mediated fevers are often considered in the differential diagnosis in many of these patients. In those resistant to acetaminophen, non-steroidal anti-inflammatory drugs (e.g. ibuprofen) should be considered when bleeding is not a primary concern. Cooling blankets can be useful, but control of shivering is necessary since it can aggravate intracranial hypertension.19 Newer intravascular cooling devices provide an exciting alternative to more rapidly and consistently fever control in this brittle patient group. Independent of the cooling method, if shivering complicates its use, it can be controlled with various medications such as meperidine, parenteral sedatives, and neuromuscular paralysis. The key point about fever control in patients with brain swelling and/or intracranial hypertension is that it is essential and requires close follow-up to assure that it is brought under control in a timely fashion.

Coughing and straining against the ventilator increases intrathoracic pressure and can reduce the venous outflow from the intracranial cavity leading to elevation of the ICP. As a result, strategies to decrease these ventilator (or airway) provoked problems can be essential to the management of patients with brittle intracranial hypertension. Some of these strategies include repositioning of the endotracheal tube, inhaled nebulizations that can serve to decrease coughing, ventilator adjustments adapted to the patient’s respiratory behavior, or the administration of sedation or non-depolarizing neuromuscular blockers.

Positive end expiratory pressure (PEEP) will increase ICP only when mean airway pressures are increased, causing transmission to the mediastinum. When pulmonary compliance is reduced as occurs in adult respiratory distress syndrome or pneumonia, the effect of PEEP on ICP is attenuated. Probably more important than the effect of PEEP on ICP is its potential effect to decrease cardiac output and blood pressure with their deleterious impact on cerebral perfusion. In general, the use of direct ICP monitoring will identify patients at risk for PEEP-induced ICP elevations.

Frequent or continuous monitoring of systemic blood pressure is a cornerstone of ICP management in patients with intracranial hypertension. Hypotension will directly cause cerebral vasodilatation and increase ICP. A treatment plan should be generated which includes the use of pressor agents and hypotonic fluids at the bedside to allow rapid intervention at the first observation of significant relative blood pressure lowering. When cerebral autoregulatory mechanisms are impaired, however, hypertension may lead to pathological increases in regional CBF, worsened brain swelling, and aggravation of intracranial hypertension, as outlined above.

Pain and arousal can cause elevated ICP by increasing CBF. As a result, patients with life-threatening intracranial hypertension should generally receive sedatives and analgesics even if their use risks “clouding” of the neurologic exam. The present availability of short-acting sedatives and analgesics and the ready availability of neuroimaging have simplified the historical reluctance to utilize these class of agents in the neurologically ill.

Seizures increase ICP by increasing cerebral metabolism and CBF by Valsalva. If the patient is deemed to be at risk, anticonvulsants should be administered promptly. Given the deleterious consequences of seizures and the severity of illness of these patients, drugs that can be parenterally administered and with known effectiveness as a monotherapy should be used first. Since hypotension can accompany the administration of phenytoin and phenobarbital, close monitoring of the blood pressure is critical with preparedness to detect any relative blood pressure lowering and promptly intervene.

Mechanical ventilation and hyperventilation

Hyperventilation induces a rapid and effective reduction in ICP through vasoconstriction induced by hypocapnia-associated CSF alkalosis.20 The duration of the ICP reduction is variable, but, in general, the ICP returns to baseline within hours after commencing hyperventilation due to normalization of the CSF alkalosis through compensatory adjustments in the bicarbonate buffering systems in the brain and vascu-
lar smooth muscle.

When hyperventilation is required for urgent management, it can be accomplished with an Ambu mask or mechanical ventilation. Providing a 10–12 cc/kg tidal volume at a rate of 14–20 breaths/minute usually achieves substantial reduction in the pCO2. Note, that the ideal pCO2 value is variable depending on the clinical situation and the individual patient’s response. One of the most controversial questions is whether excessive hyperventilation can cause cerebral ischemia through extreme cerebral vasoconstriction, a phenomenon suggested by several studies in traumatic brain injured patients. The most recent work on the subject in patients with severe traumatic brain injury utilizing positron emission tomography demonstrated that hyperventilation can be safely performed (without consequent cerebral ischemia) to a pCO2 of 30 mmHg, and, perhaps, to ~5 mmHg in selected patients. Furthermore, it has been shown that hyperoxia can improve oxygen delivery to the brain during hyperventilation.

The potential benefits of hyperventilation must be balanced against some of its potential deleterious consequences including, but not limited to diminished cardiac filling pressures, with resultant hypotension, decreased myocardial oxygen supply with an increase in myocardial demand, elevation in mean airway pressure leading to accentuation of intracranial hypertension, electrolyte disturbances (e.g., alkalosis, hypokalemia, and hyperchloremia), and cardiac arrhythmias. Because hyperventilation is the most rapid way to reduce ICP, it is best kept as a “trick up the sleeve” for emergent ICP elevations. A modest and safe goal is a pCO2 of 30 mmHg seems safest with the present state of our knowledge, and preoxygenation may add a layer of protection potentially susceptible to ischemia form the hyperventilation. Once alternative ICP lowering strategies are instituted controlling ICP and CPP adequately, hyperventilation should be lifted. However, gradual withdrawal of hyperventilation is necessary to avoid rebound elevations in ICP as the pCO2 is normalized. We recommend not exceeding pCO2 increases of 2–3 mmHg per hour. When hyperventilation is used for a prolonged period, jugular venous oxygen saturation can be used to monitor for the feared complication of cerebral ischemia from this maneuver. Of note is that inadvertent fluctuations in pCO2, i.e., due to variable ventilation during transport, are an important and avoidable cause of ICP plateaus and pressure waves. We recommend using transport ventilators and Ambu bagging the patient with the same ventilator frequency when brittle intracranial hypertension is present to minimize variations in pCO2 during transport.

Tromethamine (THAM) is a buffer than can be used to correct acidotic states, and it can be used, at times, to assist in the management of patients with intracranial hypertension. The advantage of THAM is that it alkalinizes without changing plasma sodium or pCO2. THAM may have a role in limiting rebound ICP elevation during the withdrawal of hyperventilation or prolonging benefit of hyperventilation in some. It is administered intravenously at a dose of 1 cc/kg/hour; some of the complications associated with its use include local skin irritation and necrosis, hypoglycemia, and respiratory depression.

CSF drainage

CSF drainage with a ventricular catheter is the primary treatment for hydrocephalus, and it can be a useful treatment strategy for intraventricular hemorrhage through both CSF drainage and providing access for administration of intraventricular thrombolytic agents. While CSF drainage through lumbar puncture should generally be avoided in patients with intracranial hypertension, it is a mainstay of treatment for patients with pseudotumor cerebri (benign intracranial hypertension).

Mannitol

Osmotherapy is directed at increasing plasma osmolality, establishing an osmotic gradient across the relatively impermeable blood-brain-barrier. This favors a net loss of brain water thereby increasing brain compliance and decreasing ICP. In addition, mannitol, the most widely used osmotic agent, can improve cerebral perfusion through transient hypervolemia and hemodilution leading to autoregulatory cerebral vasoconstriction, decreased cerebral blood volume, and lower ICP and it increases to some extend CSF absorption. However, most mechanisms of brain injury lead to disruption of the blood brain barrier and a loss of normal autoregulation and as a result, osmotic agents are less effective in injured brain regions. This is an important consideration when strategizing management in individual patients with unilateral mass lesions and BTD.

Mannitol is typically used in its 20% solution. Its ICP lowering effect is dose-dependent, and it appears to be maximal with a ~1 g/kg dose infused over 30 minutes. But the duration of benefit from this high dose infusion is limited to several hours and terminal dose-interval ICP elevations beyond the pre-treatment baseline is common. Smaller doses of 0.25–0.5 g/kg over longer infusion periods (~30–60 minutes) can be associated with less profound and more lasting ICP benefit within the usual four hour dose interval when multi-dosing regimens are used. The reduction in ICP after mannitol use should be apparent within 15 minutes, and failure of a response to mannitol is considered ominous, but not hopeless in our experience.

The goal of osmotherapy should be plasma hyperosmo-
lality with maintenance of adequate intravascular volume. In general, the target osmolality should be in the 300–310 mOsm/L range with adequate maintenance intravenous fluid administration. Normal saline should be used for maintenance and replacement fluids. Hypotonic fluids are contraindicated and should be avoided because water accumulation by hyperosmolar brain can aggravate brain swelling and intracranial hypertension. The development of moderate hypernatremia should be expected and tolerated because administering of hypertonic fluids to correct the hypernatremia is counter-productive and potentially dangerous.

Single doses of mannitol are often effective in reducing ICP and improving intracranial compliance temporarily. When single doses are used, monitoring of the plasma osmolality is unimportant. The benefit of multi-dosing regimens is more controversial. This is due to some of the experimental evidence it can accentuate regional brain water when the blood brain barrier is disrupted. In addition, its disproportionate impact on uninjured brain (relative to injured) can potentially accentuate BTD through enhancement of regional intracranial pressure differentials. Nonetheless, mannitol is an effective agent for rapidly reducing ICP in an emergency setting, and it can buy critical time to temporarily stabilize the patient while other treatment strategies are being arranged and commenced.

Rapid diuresis before administration of adequate amounts of replacement fluids can occur in some patients after receiving mannitol. This can lead to systemic hypotension, emphasizing the need for preparedness when using this treatment modality. We always have pressor agents and replacement fluids readily available at the bedside in patients with increased ICP. Other important complications include electrolyte disturbances (hypernatremia and hypokalemia), pre-renal azotemia, and congestive heart failure. Sometime, pre-treatment with a dose of furosemide can circumvent some of the complications of the transient expansion of intravascular volume that occurs immediately after administration of mannitol.

Hypertonic saline

Hypertonic saline has been used with renewed enthusiasm in patients with brain swelling and intracranial hypertension. The osmolality of 3% saline (1,026 mOsm/L) is similar to that of 20% mannitol (1,375 mOsm/L). The osmolality is much higher with other solutions such as 7.5% saline (2,565 mOsm/L) and 23.4% saline (8,008 mOsm/L). Variable formulations of hypertonic saline have been used with different size boluses (up to 75 cc) with clinical benefit. Its use can be associated with the expected complications of hypernatremia, hypokalemia, hyperchloremia, coagulopathy, and congestive heart failure. Hypertonic saline infusions are an underrecognized part of the ICP lowering armamentarium. Its use can be a particularly well-suited treatment in patients with volume depletion or renal failure.

Loop diuretics

Loop diuretics such as furosemide can reduce ICP and have been reported in selected series at reducing ICP alone or when used in conjunction with osmotic agents. Diuretics exert their effect through an osmotic gradient caused by a mild diuresis, reduction in CSF formation, and reduction in brain water. They provide another alternative when mild reductions in ICP are desired. However, like osmotic agents, they can produce volume and electrolyte depletion, requiring proper treatment and surveillance for these complications.

Corticosteroids

Corticosteroids have been shown to reduce the vasogenic edema associated with brain tumors and abscesses, but their benefit with other processes that can cause intracranial hypertension is less clear. There is generally no benefit consistently demonstrated with intracerebral hemorrhage. While it may have a theoretic advantage in certain stages of infarction related edema, it has not been of demonstrated benefit and has been associated with worse outcome. Dexamethasone is the most commonly used corticosteroid for vasogenic cerebral edema, and there is a wide range of dosing alternatives: we typically use 16–24 mg/day of dexamethasone in 2–4 divided doses in extreme situations, it can be given parenterally or enterically. Higher doses can be safely used for brief periods of time with less clear benefit over more conventional dosing. Potential side-effects include gastrointestinal bleeding, hyperglycemia, disturbance in nitrogen metabolism, wound breakdown and poor wound healing, and behavioral disturbances. The hyperglycemia is of particular concern and requires aggressive intervention due to its increasingly recognized negative impact on outcome with most of the processes that can cause intracranial hypertension.

Hypothermia

There has been renewed interest in moderate hypothermia (32–34 degrees Centigrade) as an adjunctive therapy for patients with intracranial hypertension. It can lower ICP and improve CPP in some patients, and it theoretically limits hypoperfusion brain injury due to its neuroprotective properties. However, it has not yet been demonstrated to achieve outcome benefit in scientifically valid clinical trials. In spite of the lack of scientific evidence for its benefit to date, those experienced in the management of patients with the problem have used hypothermia with success in selected patients; it is considered a useful “time-buying” trick in refractory cases.
The most classical method for hypothermia induction is with cooling blankets placed above and below the patient with the variable addition of ice water lavage. However, newer intravascular cooling are increasingly available but not yet widely applied.\textsuperscript{13} When hypothermia is used, shivering can be a complicating factor when the body temperature sinks below 36 degrees Centigrade. Since shivering can increase ICP, its occurrence should be anticipated and sedatives and/or narcotics should be rapidly administered titrated to effect to limit its severity. Rebound intracranial hypertension is an important concern during the rewarming process.\textsuperscript{50} When induced hypothermia is terminated, patients should be allowed to passively re-warm slowly with close attention to slow down its pace if the patient develops a rebound increase in ICP. The most common complications of induced hypothermia include pneumonia, cardiac arrhythmia, and coagulopathy.\textsuperscript{51}

**Propofol and barbiturate coma**

Propofol can induce a significant drop in ICP while preserving CPP under physiologic brain dynamics, most likely from an induced decline in cerebral metabolic rate. However, currently systemic data do not exist and the clinical value of propofol, if utilized, needs to be addressed on an individual patient’s basis. Side effects of propofol use include hypotension with higher dosage, predisposition to (Gram-negative) infection, hypertriglycerideremia, metabolic acidosis, myopathy, and possible idiosyncratic reactions.

The use of barbiturate coma is an advanced treatment measure aimed at preventing patient demise from uncontrollable intracranial hypertension. While it has been used with variable degrees of success for the treatment of elevated ICP from a variety of causes, there is little evidence that it improves outcome.\textsuperscript{52-56} In addition, it is a costly undertaking from an economic and physiological perspective. Some of its ICP lowering benefits of barbiturates may be derived from depression of cerebral metabolism and reduction of CBF in normal areas of brain, with shunting of blood to ischemic areas. In addition, it may limit oxidative damage to lipid membranes and scavenge free radicals, reduce formation of vasogenic edema, attenuate fatty acid release, reduce intracellular calcium, and, of course, limit external stimuli from causing patient arousal with the concomitant increases in CBF and cerebral blood volume.\textsuperscript{48,54}

The induction of barbiturate “coma” is a weighty undertaking and demands experience to assure its safe and proper use. The agents most commonly used are thiopental and pentobarbital. Systemic hypotension, complications of prolonged immobility and mechanical ventilation, and immune suppression are the most common deleterious effects of barbiturate therapy. In addition, the need for more frequent transport and invasive line complications are other risks that should not be underestimated in their potential impact. Pentobarbital coma requires a loading dose of 10–30 mg/kg. In our experience, it is best to administer the pentobarbital in small boluses of 100–200 mg every 10–20 minutes as tolerated from a blood pressure standpoint. This should be done under electroencephalographic (EEG) monitoring. While each bolus will briefly achieve either a burst-suppression pattern or a flat EEG, usually a more full loading dose is necessary to achieve a sustained effect. A continuous drip of 1–3 mg/kg/hour is usually necessary to maintain the desired depth of anesthesia. Optimizing depth of barbiturate therapy should be guided by EEG in these cases, usually titrating a continuous drip to achieve a burst suppression pattern in the 3–6 bursts/minute frequency. The EEG can be monitored continuously or hourly, and ICU nurses can be taught to interpret burst-suppression frequency as part of the bedside monitoring.

In patients under prolonged barbiturate anesthesia, various strategies must be used to compensate for the loss of neurological examination and can include continued evoked potential monitoring, serial imaging studies, and numerous other devises increasingly available that that can track a number of combinations of intracranial factors. The only neurological change that is often useful in these patients is pupillary dilation, since the barbiturates usually cause bilaterally small pupils. When they become large, it can be an ominous sign. However, an important phenomenon has been described in patients under pentobarbital coma: an accentuated ciliospinal reflex that manifests as large (>6 mm), seemingly unreactive, pupils to light usually after a nursing maneuver such as patient turning. It can be misinterpreted as a catastrophic clinical change leading to unnecessary scans. Usually, when it occurs, the pupils will react with a sustained intense light stimulus, and it spontaneously abates within minutes after its occurrence.\textsuperscript{57}

As already mentioned, intensive hemodynamic monitoring is required with barbiturate coma. Since volume depletion increases the risk of hypotension from barbiturates, special attention should focus on maintaining intravascular volume with the guidance of invasive monitoring in most cases. The risk of infection and the concurrent disruption in the usual response to infection, fever, requires systematic surveillance for infection with regular cultures (at least every other day) of the endotracheal secretions, urine, and blood drawn through invasive lines. Hypothermia is common with barbiturates, and, in fact, we often use barbiturates to facilitate the induction of hypothermia as a treatment modality. While permissive moderate hypothermia is recommended when using barbiturates, extreme hypothermia (<32 degrees Centigrade) is associated with numerous complications and should be avoided.
The long half-life of pentobarbital (approximately 24 hours) allows a slow recovery even when abruptly stopped. Shivering is common during the recovery period from barbiturate anesthesia and may require treatment with narcotics or short-acting sedatives. We prefer to use propofol for this complication. In addition, chaotic EEG patterns are common during this period and often misinterpreted as status epilepticus.

Surgical procedures

Surgical procedures can be a very important part of the management of patients with intracranial mass lesions, with or without intracranial hypertension. The two primary types of procedures are removal of the primary problem (e.g., hematoma evacuation, neoplasm excision, etc.) or creating more room to accommodate an intracranial mass and deter the deleterious effects of BTD through removing skull bone and opening the overlying dura ipsilateral to the mass through hemicraniectomy and durotomy (Fig. 5A, B). The application of these surgical alternatives and their timing is heuristic based on numerous clinical factors, the use of hemicraniectomy to treat patients with large supratentorial cerebral hemispheric infarctions (LHI) is discussed next.

While LHI are not common (accounting for less than 10% of all ischemic strokes), they are amongst the most disabling and deadly. As a result, physicians involved with the management of these patients must be equipped with a contemporary management strategy to minimize disability and mortality in patients in whom survival is embraced as the appropriate medical care focus in keeping with the patient’s life philosophy. LHI defines a group of patients with a disabling stroke, variable degrees of collateral circulation, and at risk for “malignant MCA infarction” with associated brain swelling and life threatening deterioration from brain herniation and intracranial hypertension.

In addition to the usual priorities of general systemic care (e.g., respiratory, cardiovascular, nutritional) and general stroke care (e.g., blood sugar control, fever management, deep vein thrombosis prophylaxis), patients who suffer a LHI should receive thoughtful application of medical treatments and monitoring for optimizing brain perfusion (or avoiding cerebral hypoperfusion), minimizing brain swelling, and limiting brain tissue shifts as discussed above. There should be early patient/family/surrogate discussions regarding the patient’s life priorities as they may apply to practical life-and-death decision-making and procedures in the context of the disabling stroke event, a strategic monitoring plan for early detection of deterioration and brain swelling, and engagement of other professionals necessary for the timely application of treatments necessary in the case of important worsening (e.g., neurosurgeons).

There have been a variety of clinical predictors studied and identified to correlate with fatal outcome from LHI. Some of these factors include high NIHSS scores, early drowsiness, and early nausea and vomiting. The various identified prognostic factors are generally associated with larger infarctions, and, not surprisingly, computed tomography (CT) and magnetic resonance imaging (MRI) analyses have confirmed a correlation between infarction volume and outcome from supratentorial infarctions. While new evolving approaches to predicting brain swelling in patients with LHI are exciting and our wisdom on their best application will evolve further over time, at this point all acute patients with LHI should be considered at risk for severe, life-threatening deterioration. In a prospective randomized pilot clinical trial on LHI and surgical decompression 65% of the registered patients with at least complete MCA territory infarction (based on acute clinical and CT imaging criteria) developed life-threatening brain swelling and tissue shifts (>7 mm of anteroseptal shift or >4 mm of pineal shift from midline) within 96 hours of stroke onset.

While patients with acute ischemic stroke are a heterogeneous group with variable baseline blood pressure and stroke mechanisms, those with patients with LHI more likely have a large vessel narrowing/occlusions, autoregulatory dysfunction, and/or are vitally dependent on collateral circulation. At this point in our understanding, blood pressure lowering should only be done with great reluctance in patients with LHI with clearly prioritized goals, thoughtful agent selection, and vigilant monitoring to avoid over-treatment. Depending on the extent of brain swelling and the degree of blood pressure lowering desired, it may be rational and appropriate to consider parenchymal ICP or CBF monitoring to avoid exacerbating regional cerebral hypoperfusion. In most cases, we recommend maintenance of the blood pressure at least in the high normal range with LHI in order to maintain collateral perfusion and cerebral edema progressively challenges this vital brain preserving source of cerebral blood flow.

It has been shown that the majority of patients who deteriorate from LHI do not have important ICP elevations or cerebral hypoperfusion as an early contributing factor to their worsening. Their clinical deterioration is mainly due to BTD from evolving brain pressure differentials caused by regional cerebral edema. Therefore, indiscriminant administration of mannitol or us of controlateral ventricular drain insertion (the ipsilateral ventricle is usually collapsed) can lead to accentuation of the pressure differentials that drive BTD and augment the clinical worsening. However, early ICP elevation, when it does occur with LHI, stratifies the patient to higher risk of death from brain swelling, and younger patients are at higher risk for such early elevations. It
has not been shown that ICP focused management (whether or not under the guidance of ICP monitoring) improves the outcome in LHI patients as standardized medical treatment protocols differ among study center. In fact, some of the more widely quoted studies on LHI with aggressive ICP lowering-focused treatment strategies report some of the most dismal outcomes for this disease.

We use ICP monitoring in young patients with LHI who already have shown evidence of significant regional brain swelling and compression of ipsilateral cerebrospinal fluid spaces. These patients have quickly declining intracranial compliance and are at risk for ICP plateau waves. The presence of early ICP elevation in the young patient puts everyone on “red alert” to the escalating risk of death in that individual patient: this information can be used to factor into the decisions regarding treatment escalation and the possible application and timing of surgical decompression. In addition, ICP monitoring in such patients may assist with strategies (positioning and medical) to improve intracranial compliance and attempt to avoid catastrophic cerebral hypoperfusion during transport and various nursing maneuvers. When ICP monitoring is employed, we recommend using an ipsilateral (to the infarction) parenchymal monitor since it will be the region of greatest ICP elevation. The ipsilateral placement is because the ICP will be maximal in the region of dominant brain swelling, the ventricle ipsilateral to the infarction collapses as swelling progresses with the various disadvantages mentioned earlier in this section.

When ICP is elevated, medical management alone carries a high mortality. However, with respect to ICP reduction, the application of conventional ICP lowering strategies can be very helpful early in the course of management.
clude optimizing head and body positioning, avoidance of behaviors that elevate ICP in patients with poor cerebral compliance (fighting the ventilator, agitation, seizures), tight fever control (see section), hyperventilation and the application of mannitol. We rarely administer multidosing regimens of mannitol in LHI patients as its misapplication and overuse has hypothetical dangers in these patients. When ICP elevations are considered important to medically treat in patients with LHI, hypertonic saline can also be a very effective strategy. Fluid management should avoid volume depletion as there is no role for dehydration as a management strategy to limit the development of brain edema. Isotonic (0.9%) saline infusions are generally recommended without clear scientific evidence for their unique advantage for patients with LHI. When patients are exposed to hyperosmolar treatments, then the use of only isotonic fluids is critical as the hyperosmolar brain may be at risk for worsened cerebral edema when exposed to hypotonic fluids. There is some evidence of a possible benefit of albumin infusions in experimental animals with LHI from MCA occlusion, but this has not been widely applied in humans.69,70

The potential for surgical decompression as a method to limit infarct volume and mortality from brain swelling after stroke has been demonstrated in experimental animals with more recently promising human work.68,71-73 Unfortunately, the selection of patients for this procedure and its best timing is still not well defined: the decision-making for this step requires a delicate balancing between the patient’s medical reality, pace and anticipated severity of clinical progression, prognosis, pre-morbid patient wishes, and various ethical and psychosocial issues. Very recently, the combined, pooled analysis of 3 large, European hemicraniectomy trials in LHI was reported.74 All 3 studies (the terminated studies DESTINY and DECIMAL and the still ongoing study HAMLET) restricted enrollment to patients of <60 years of age and timing of surgery to <48 hours after stroke onset. A total of 93 patients were randomized to surgical and medical therapy and evaluated with the modified Rankin Scale (mRS) at 1 year. Hemicraniectomy more than doubled the changes of survival, from 29% to 78% which resulted in a significant absolute risk deduction of 49% translating into a number needed to treat of 2 to avoid one death. The proportion of patients with minimal-to-moderate disability (that is, mRS 0 to 3) was significantly increased from 21% to 43%. Discussing the anticipated outcome of hemicraniectomy in LHI with families the results can be presented that for every 10 procedures performed 5 will escape death and at 1-year one patient will have mild, 1 will have moderate, and 3 will have moderate-to-severe disability. The analysis found no additional benefit with surgery performed within 24 hours compared to surgery performed later. Importantly, the data also indicated that infarction of the dominant hemisphere is no longer an acceptable for withholding hemicraniectomy as aphasia from left-dominant lesions can significantly improve whereas neglect from nondominant lesions is known to limit the degree of post-stroke reintegration, active participation, and rehabilitation.

Summary

Intracranial hypertension is the final common pathway of morbidity and mortality for diverse neurological problems, and its proper treatment requires the timely application of the available therapeutic alternatives when the clinical situation and prognosis warrants and justifies treatment. Anticipating patients at risk for brain swelling is important and allows the development of a strategic plan to limit its severity and facilitate early intervention when possible. The initial therapeutic focus for ICP reduction should be the control of factors that can aggravate intracranial hypertension such as inappropriate head and body position, elevated body temperature, inadequate treatment of pain and agitation, elevated airway pressures, blood pressure fluctuations, seizures, and administration of hypotonic fluids. The appropriate conventional medical therapies should be selected based on the details of each specific case. It should be clear that BTD and intracranial hypertension are not synonymous, and the treatment of each of them can be different. Surgical removal of an intracranial mass lesion or expansion of the intracranial compartment should be considered in patients with severe BTD and/or evolving intracranial hypertension. Hemicraniectomy with durotomy should be considered in patient with LHI. In the end, the treatment of intracranial hypertension is heuristic, challenging the managing physician’s to define the optimal level of care for each individual patient. Further, successful management depends on a partnership with nurses founded on comprehensive communication to assist with the accurate translation of the defined care priorities.

REFERENCES


