Management of Intracranial Hypertension

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Intracranial hypertension is a common neurologic complication in critically ill patients; it is the common pathway in the presentation of many neurologic and nonneurologic disorders. The underlying pathophysiology of increased intracranial pressure (ICP) is the subject of intense basic and clinical research, which has led to advances in understanding the physiology related to ICP. Few specific treatment options for intracranial hypertension have been subjected to randomized trials, however, and most management recommendations are based on clinical experience.

Intracranial pressure

Normal values

In normal individuals with closed cranial fontanelles, the central nervous system contents, including the brain, spinal cord, blood, and cerebrospinal fluid (CSF), are encased in a noncompliant skull and vertebral canal, constituting a nearly incompressible system. The system has a small amount of capacitance provided by the intervertebral spaces. In the average adult, the skull encloses a total volume of 1475 mL, including 1300 mL of brain, 65 mL of CSF, and 110 mL of blood [1]. The Monroe-Kellie hypothesis states that the sum of the intracranial volumes of blood, brain, CSF, and

other components is constant, and that an increase in any one of these must be offset by an equal decrease in another, or else pressure increases. An increase in pressure caused by an expanding intracranial volume is distributed evenly throughout the intracranial cavity [2,3].

The normal range for ICP varies with age. Values for pediatric patients are not as well established. Normal values are less than 10 to 15 mm Hg for adults and older children, 3 to 7 mm Hg for young children, and 1.5 to 6 mm Hg for term infants. ICP can be subatmospheric in newborns [4]. For the purpose of this article, normal adult ICP is defined as 5 to 15 mm Hg (7.5–20 cm H_2O). ICP values of 20 to 30 mm Hg represent mild intracranial hypertension; however, when a temporal mass lesion is present, herniation can occur with ICP values of less than 20 mm Hg [5]. In most circumstances, ICP values of greater than 20 to 25 mm Hg require treatment. Sustained ICP values of greater than 40 mm Hg indicate severe, life-threatening intracranial hypertension.

Cerebral dynamics overview

Cerebral perfusion pressure (CPP) depends on mean systemic arterial pressure (MAP) and ICP, as defined by the following relationship:

$$CPP = MAP - ICP, \text{ where MAP} = (1/3 \text{ systolic BP}) + (2/3 \text{ diastolic BP})$$

As a result, CPP can be reduced by an increase in ICP, a decrease in blood pressure, or a combination of both factors. Through the normal regulatory process called pressure autoregulation, the brain is able to maintain a normal cerebral blood flow (CBF) with a CPP ranging from 50 to 150 mm Hg. At CPP values of less than 50 mm Hg, the brain may not be able to compensate adequately, and CBF falls passively with CPP. After injury, the ability of the brain to pressure autoregulate may be absent or impaired and, even with a normal CPP, CBF can passively follow changes in CPP.

When CPP is within the normal autoregulatory range (50–150 mm Hg), this ability of the brain to pressure autoregulate also affects the response of ICP to a change in CPP [6–8]. When pressure autoregulation is intact, decreasing CPP results in vasodilation of cerebral vessels, which allows CBF to remain unchanged. This vasodilation can result in an increase in ICP, which further perpetuates the decrease in CPP. This response has been called the vasodilatory cascade. Likewise, an increase in CPP results in vasoconstriction of cerebral vessels and may reduce ICP. When pressure autoregulation is impaired or absent, ICP decreases and increases with changes in CPP.

Intracranial hypertension

Causes of intracranial hypertension

The different causes of intracranial hypertension (Box 1) can occur individually or in various combinations. In primary causes of increased ICP, its

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Box 1. Causes of intracranial hypertension

Intracranial (primary)
Brain tumor
Trauma (epidural and subdural hematoma, cerebral contusion)
Nontraumatic intracerebral hemorrhage
Ischemic stroke
Hydrocephalus
Idiopathic or benign intracranial hypertension
Other (eg, pseudotumor cerebri, pneumocephalus, abscess, cyst)

Extracranial (secondary)
Airway obstruction
Hypoxia or hypercarbia (hypoventilation)
Hypertension (pain/cough) or hypotension
  (hypovolemia/sedation)
Posture (head rotation)
Hyperpyrexia
Seizure
Drug and metabolic (eg, tetracycline, rofecoxib, divalproex
  sodium, lead intoxication)
Others (eg, high-altitude cerebral edema, hepatic failure)

Postoperative
Mass lesion (hematoma)
Edema
Increased cerebral blood volume (vasodilation)
Disturbance of CSF

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normalization depends on rapidly addressing the underlying brain disorder. In the second group, intracranial hypertension is due to an extracranial or systemic process that is often remediable [9–11]. The last group comprises the causes of increased ICP after a neurosurgical procedure.

Intracranial hypertension secondary to traumatic brain injury

Special features should be considered in patients who have traumatic brain injury (TBI), in which lesions may be heterogeneous, and several factors often contribute to increase the ICP [12]:

Traumatically induced masses: epidural or subdural hematomas, hemorrhagic contusions, foreign body, and depressed skull fractures
Cerebral edemas [13]
Hyperemia owing to vasomotor paralysis or loss of autoregulation [14]

Hypoventilation that leads to hypercarbia with subsequent cerebral vasodilation

Hydrocephalus resulting from obstruction of the CSF pathways or its absorption

Increased intrathoracic or intra-abdominal pressure as a result of mechanical ventilation, posturing, agitation, or Valsalva's maneuvers

After evacuation of traumatic mass lesions, the most important cause of increased ICP was thought to be vascular engorgement [14]. Recent studies have suggested that cerebral edema is the primary cause in most cases [15].

A secondary increase in the ICP is often observed 3 to 10 days after the trauma, principally as a result of a delayed hematoma formation, such as epidural hematomas, acute subdural hematomas, and traumatic hemorrhagic contusions with surrounding edema, sometimes requiring evacuation [16]. Other potential causes of delayed increases in ICP are cerebral vasospasm [17], hypoventilation, and hyponatremia.

Neurologic intensive care monitoring

Intracranial hypertension is an important cause of secondary injury in patients who have acute neurologic and neurosurgical disorders and typically mandates specific monitoring. Patients who have suspected intracranial hypertension, especially secondary to TBI, should have monitoring of ICP; monitoring of cerebral oxygen extraction, as with jugular bulb oximetry or brain tissue Po_2, may also be indicated. Brain-injured patients should also have close monitoring of systemic parameters, including ventilation, oxygenation, electrocardiogram, heart rate, blood pressure, temperature, blood glucose, and fluid intake and output. Patients should be monitored routinely with pulse oximetry and capnography to avoid unrecognized hypoxemia and hypoventilation or hyperventilation. A central venous catheter is commonly needed to help evaluate volume status, and a Foley catheter is used for accurate urine output.

Intracranial pressure monitoring

Clinical symptoms of increased ICP, such as headache, nausea, and vomiting, are impossible to elicit in comatose patients. Papilledema is a reliable sign of intracranial hypertension, but is uncommon after head injury, even in patients who have documented elevated ICP. In a study of patients who had head trauma, 54% of patients had increased ICP, but only 3.5% had papilledema on fundoscopic examination [18]. Other signs, such as pupillary dilation and decerebrate posturing, can occur in the absence of intracranial hypertension. CT scan signs of brain swelling, such as midline shift and compressed basal cisterns, are predictive of increased ICP, but intracranial hypertension can occur without these findings [19].

Types of monitors

The ventriculostomy catheter is the preferred device for monitoring ICP and the standard against which all newer monitors are compared [20]. An intraventricular catheter is connected to an external pressure transducer by way of fluid-filled tubing. The advantages of the ventriculostomy are its low cost, the option to use it for therapeutic CSF drainage, and its ability to recalibrate to minimize errors owing to measurement drift. The disadvantages are difficulties with insertion into compressed or displaced ventricles, inaccuracies of the pressure measurements because of obstruction of the fluid column, and the need to maintain the transducer at a fixed reference point relative to the patient's head. The system should be checked for proper functioning at least every 2 to 4 hours, and with any change in the ICP, neurologic examination, or CSF output. This check should include assessing for the presence of an adequate waveform, which should have respiratory variations and transmitted pulse pressure.

When the ventricle cannot be cannulated, alternatives can be used. Different non–fluid-coupled devices are available for ICP monitoring and have replaced the subarachnoid bolt. The microsensor transducer and the fiber optic transducer are the most widely available. These transducer-tipped catheters can be inserted into the subdural space or directly into the brain tissue [21]. The main advantages of these monitors is the ease of insertion, especially in patients who have compressed ventricles; however, none of the transducer-tipped catheters can be reset to zero after they are inserted into the skull, and they exhibit measurement drift over time [22]. Subdural and epidural monitors for ICP measurements are less accurate, when compared with ventriculostomy or parenchymal monitors.

For surgical patients, the ICP monitor may be inserted at the end of the surgical procedure. ICP monitoring is continued for as long as treatment of intracranial hypertension is required, typically 3 to 5 days. A secondary increase in ICP may be observed 3 to 10 days after trauma in 30% of patients who have intracranial hypertension [16] secondary to development of delayed intracerebral hematoma, cerebral vasospasm, or systemic factors such as hypoxia and hypotension.

Types of intracranial pressure waveforms

The variations seen in the normal tracing of ICP originate from small pulsations transmitted from the systemic blood pressure to the intracranial cavity. These blood pressure pulsations are superimposed on slower oscillation caused by the respiratory cycle. In mechanically ventilated patients, the pressure in the superior vena cava increases during inspiration, which reduces venous outflow from the cranium, causing an elevation in ICP.

Pathologic waveforms

As the ICP increases, cerebral compliance decreases, arterial pulses become more pronounced, and venous components disappear. Pathologic waveforms include Lundberg A, B, and C types. Lundberg A waves, or plateau waves, are ICP elevations to more than 50 mm Hg lasting 5 to 20 minutes. These waves are accompanied by a simultaneous increase in MAP, but it is not clearly understood if the change in MAP is a cause or effect. Lundberg B waves, or pressure pulses, have an amplitude of 50 mm Hg and occur every 30 seconds to 2 minutes. Lundberg C waves have an amplitude of 20 mm Hg and a frequency of 4 to 8 per minute; they are seen in the normal ICP waveform, but high-amplitude C waves may be superimposed on plateau waves [23].

Indications for intracranial pressure monitoring

Monitoring of ICP is an invasive technique and has some associated risks. For a favorable risk-to-benefit ratio, ICP monitoring is indicated only in patients who have significant risk for intracranial hypertension (Box 2) [12]. Patients who have TBI and are particularly at risk for developing an elevated ICP include those with Glasgow Coma Scale of 8 or less after cardiopulmonary resuscitation and those who have an abnormal admission head CT scan. Such abnormalities might include low-density or high-density lesions, including contusions; epidural, subdural, or intraparenchymal hematomas; compression of basal cisterns; and edema [24]. Patients who are able to follow commands have a low risk for developing intracranial hypertension, and serial neurologic examinations can be followed.

Although CT scan findings are not accurate in determining the actual ICP, the risk for developing intracranial hypertension can be predicted. Sixty percent of patients who have a closed head injury and an abnormal CT scan have intracranial hypertension. Only 13% of patients who have

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Box 2. Indications for intracranial pressure monitoring

Glasgow Coma Scale score: 3–8 (after resuscitation)
1. Abnormal admission head CT scan
   a. Hematoma
   b. Contusion
   c. Edema
   d. Herniation
   e. Compressed basal cistern
2. Normal admission head CT scan plus two or more of the following
   a. Age older than 40
   b. Motor posturing
   c. Systolic blood pressure less than 90 mm Hg

a normal CT scan have elevated ICP, except for patients who have certain risk factors, including age more than 40 years old, systolic blood pressure less than 90 mm Hg, and decerebrate or decorticate posturing on motor examination. Patients who have a normal CT scan have a 60% risk for intracranial hypertension if they have two risk factors and 4% if they have only one risk factor. Patients who have a Glasgow Coma Scale score greater than 8 might also be considered for ICP monitoring if they require treatment that would not allow serial neurologic examinations, such as prolonged anesthesia for surgery of multiple injuries or prolonged pharmacologic paralysis for ventilatory management, or if they require a treatment that might increase ICP, such as positive end-expiratory pressure (PEEP). Other, less common, indications include patients who have multiple systemic injuries with an altered level of consciousness and subsequent to removal of an intracranial mass (eg, hematoma, tumor) [12]. ICP monitoring must also be considered in nontraumatic conditions in which an intracranial mass lesion is present (eg, cerebral infarction, spontaneous intracerebral hemorrhage) and has a likelihood of expansion leading to intracranial hypertension and clinical deterioration. Monitoring lasts until ICP has been normal for 24 to 48 hours without ICP therapy.

Complications of intracranial pressure monitoring

The most common complication of ventriculostomy catheter placement is infection, with an incidence of 5% to 14%; colonization of the device is more common than clinical infection [25]. A study found no significant reduction in infection rate in patients undergoing prophylactic change of monitors before day 5, compared with those whose catheters were in place for 5 days or more [26]. Factors that are not associated with infection are insertion of the catheter in the neurologic ICU, previous catheter insertion, drainage of CSF, and use of steroids. In a group of patients who had prolonged ventricular drainage of 10 days or more, a nonlinear increase in daily infection rate was observed over the initial 4 days but remained constant, despite prolonged catheter use [27]. Use of antibiotic-coated ventriculostomy catheters has been shown to reduce the risk for infection from 9.4% to 1.3% [28]. Other complications of ventriculostomy catheters are hemorrhage (with an overall incidence of 1.4%), malfunction, obstruction, and malposition.

Intracranial pressure treatment measures: brief summary of goals of therapy

The goals of ICP treatment may be summarized as follows:

1. Maintain ICP at less than 20 to 25 mm Hg.
2. Maintain CPP at greater than 60 mm Hg by maintaining adequate MAP.
3. Avoid factors that aggravate or precipitate elevated ICP.

An overall approach to the management of intracranial hypertension is presented in Fig. 1.

General care to minimize intracranial hypertension

Prevention or treatment of factors that may aggravate or precipitate intracranial hypertension is a cornerstone of neurologic critical care. Specific factors that may aggravate intracranial hypertension include obstruction of venous return (head position, agitation), respiratory problems (airway obstruction, hypoxia, hypercapnia), fever, severe hypertension, hyponatremia, anemia, and seizures.

Optimizing cerebral venous outflow

To minimize venous outflow resistance and promote displacement of CSF from the intracranial compartment to the spinal compartment,
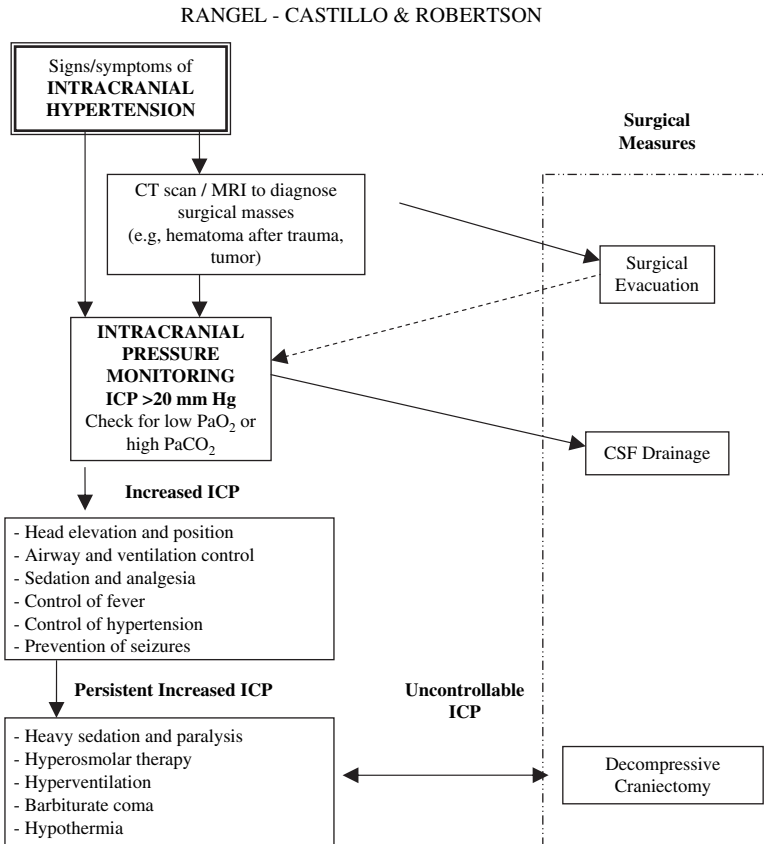
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Fig. 1. Diagnosis and treatment of intracranial hypertension.

elevating the head of the bed and keeping the head in a neutral position are standards in neurosurgical care. Some investigators have advocated keeping the patient's head flat to maximize CPP [7]. Other studies have shown a reduction in ICP without a reduction in either CPP or CBF in most patients with elevation of the head to 30° [29]. Still other investigators have observed that elevation of the head to 30° reduced ICP and increased CPP, but did not change brain tissue oxygenation [30]. The reduction in ICP afforded by 15° to 30° of head elevation is probably advantageous and safe for most patients. When head elevation is used, the pressure transducers for blood pressure and ICP must be zeroed at the same level (at the level of the foramen of Monro) to assess CPP accurately.

Increased intra-abdominal pressure, as can occur with abdominal compartment syndrome, can also exacerbate ICP, presumably by obstructing cerebral venous outflow. Several case reports have observed immediate reductions in ICP with decompressive laparotomy in such circumstances. A retrospective report indicated that, even when abdominal compartment syndrome is not present, abdominal fascial release can effectively reduce ICP that is refractory to medical treatment [31].

Respiratory failure

Respiratory dysfunction is common in patients who have intracranial hypertension, especially when the cause is head trauma. Hypoxia and hypercapnia can increase ICP dramatically, and mechanical ventilation can alter cerebral hemodynamics. Optimal respiratory management is crucial for control of ICP.

Thirty-six percent of comatose head injury patients present with hypoxia and respiratory dysfunction requiring mechanical ventilation on admission. Pneumonia and pulmonary insufficiency occur in 42% and 28%, respectively, as complications during hospitalization. In 227 spontaneously breathing patients who had neurologic disorders, mostly intracranial hypertension, North and Jennett [32] found that 60% had breathing abnormalities, including periodic respirations, tachypnea, and irregular breathing. Periodic breathing was not correlated, however, with any particular anatomic site of the neurologic injury. Periodic episodes of hypoventilation can precipitate increased ICP [33]. Controlled ventilation to maintain a normal $Paco_2$ can eliminate this cause of intracranial hypertension.

Mechanical ventilation can also have adverse effects on ICP. PEEP, which may be needed to improve oxygenation, can increase ICP by impeding venous return and increasing cerebral venous pressure and ICP, and by decreasing blood pressure, leading to a reflex increase of cerebral blood volume. For PEEP to increase cerebral venous pressure to levels that would increase ICP, the cerebral venous pressure must at least equal the ICP. The higher the ICP, the higher the PEEP must be to have such a direct hydraulic effect on ICP. The consequences of PEEP on ICP also depend on

lung compliance, and minimal consequences for ICP are usually observed when lung compliance is low, as in patients who have acute lung injury [34].

Sedation and analgesia

Agitation and pain may significantly increase blood pressure and ICP. Adequate sedation and analgesia are an important adjunctive treatment. No sedative regimen has clear advantages in this patient population. In general, benzodiazepines cause a coupled reduction in cerebral metabolic rate of oxygen ($CMRO_2$) and CBF, with no effect on ICP, whereas the narcotics have no effect on $CMRO_2$ or CBF, but have been reported to increase ICP in some patients [35]. One consideration in the choice of sedative should be to minimize effects on blood pressure because most available agents can decrease blood pressure. Hypovolemia predisposes to hypotensive side effects and should be treated before administering sedative agents. Selection of shorter-acting agents may have the advantage of allowing a brief interruption of sedation to evaluate neurologic status.

Fever

Fever increases metabolic rate by 10% to 13% per °C and is a potent vasodilator. Fever-induced dilation of cerebral vessels can increase CBF and may increase ICP. Fever during the postinjury period worsens neurologic injury in experimental models of TBI [36]. In an observational study in patients who had TBI, Jones and colleagues [37] found a significant relationship between fever and a poor neurologic outcome. Although a patient is at risk for intracranial hypertension, fever should be controlled with antipyretics and cooling blankets. Infectious causes must be sought and treated with appropriate antibiotics when present.

Hypertension

Elevated blood pressure is seen commonly in patients who have intracranial hypertension, especially secondary to head injury, and is characterized by a systolic blood pressure increase greater than diastolic increase. It is associated with sympathetic hyperactivity [38]. It is unwise to reduce systemic blood pressure in patients who have hypertension associated with untreated intracranial mass lesions because cerebral perfusion is being maintained by the higher blood pressure. In the absence of an intracranial mass lesion, the decision to treat systemic hypertension is more controversial and may need to be individualized for each patient.

When pressure autoregulation is impaired, which is common after TBI, systemic hypertension may increase CBF and ICP. In addition, elevated blood pressure may exacerbate cerebral edema and increase the risk for postoperative intracranial hemorrhage.

Systemic hypertension may resolve with sedation. If the decision is made to treat systemic hypertension, the choice of antihypertensive agent is important. Vasodilating drugs, such as nitroprusside, nitroglycerin, and nifedipine, can be expected to increase ICP and may reflexively increase plasma catecholamines, which may be deleterious to the marginally perfused injured brain. Sympathomimetic-blocking antihypertensive drugs, such as β-blocking drugs (labetalol, esmolol) or central acting α-receptor agonists (clonidine), are preferred because they reduce blood pressure without affecting the ICP. Agents with a short half-life have an advantage when the blood pressure is labile.

Treatment of anemia

Anecdotal cases have been reported of patients who have severe anemia presenting with symptoms of increased ICP and signs of papilledema, which resolve with treatment of the anemia [39]. The mechanism is thought to be related to the marked increase in CBF that is required to maintain cerebral oxygen delivery when anemia is severe. Although anemia has not been clearly shown to exacerbate ICP after TBI, a common practice is to maintain hemoglobin concentration at a minimum of 10 g/dL. In view of a large randomized trial of critically ill patients that showed better outcome with a more restrictive transfusion threshold of 7 g/dL [40], the issue of optimal hemoglobin concentration in patients who have TBI needs further study.

Prevention of seizures

The risk for seizures after trauma is related to the severity of the brain injury; seizures occur in 15% to 20% of patients who have severe head injury. Seizures can increase cerebral metabolic rate and ICP, but no clear relationship exists between the occurrence of early seizures and a worse neurologic outcome [41]. In patients who have severe TBI, 50% of seizures may be subclinical and can be detected only with continuous electroencephalographic monitoring [42]. Significant risk factors for later seizures are brain contusion, subdural hematoma, depressed skull fracture, penetrating head wound, loss of consciousness or amnesia for more than 1 day, and age 65 years or older.

In a randomized clinical trial, phenytoin reduced the incidence of seizures during the first week after trauma, but not thereafter [43]. Based on this study, seizure prophylaxis for patients who have severe brain injury is recommended for the first 7 days after injury. Treatment with anticonvulsants beyond 7 days should be reserved for patients who develop late seizures [44].

Measures for refractory intracranial hypertension

For patients who have sustained ICP elevations of greater than 20 to 25 mm Hg, additional measures are needed to control the ICP. Emergent

surgical management should be considered whenever intracranial hypertension occurs suddenly or is refractory to medical management.

Medical interventions

Heavy sedation and paralysis

Routine paralysis of patients who have neurosurgical disorders is not indicated; however, intracranial hypertension caused by agitation, posturing, or coughing can be prevented by sedation and nondepolarizing muscle relaxants that do not alter cerebrovascular resistance [45]. A commonly used regimen is morphine and lorazepam for analgesia/sedation and cisatracurium or vecuronium as a muscle relaxant, with the dose titrated by twitch response to stimulation. A disadvantage of this therapy is that the neurologic examination cannot be monitored closely; however, the sedatives and muscle relaxants can be interrupted once a day, usually before morning rounds, to allow neurologic assessments.

Major complications of neuromuscular blockade are myopathy, polyneuropathy, and prolonged neuromuscular blockade. Myopathy is associated with the use of neuromuscular blocking agents, particularly in combination with corticosteroids [46]. Polyneuropathy has been observed in patients who have sepsis and multiple organ failure. Prolonged neuromuscular blockade is seen in patients who have multiple organ failure, especially with kidney and liver dysfunction. Recommendations to minimize these complications include limiting the use and dose of neuromuscular blocking agents, train-of-four monitoring, measuring creatine phosphokinase daily, and stopping the drug daily to evaluate motor response [47].

Hyperosmolar therapy

Mannitol is the most commonly used hyperosmolar agent for the treatment of intracranial hypertension. More recently, hypertonic saline also has been used in this circumstance. A few studies have compared the relative effectiveness of these two hyperosmotic agents, but more work is needed.

Intravenous bolus administration of mannitol lowers the ICP in 1 to 5 minutes, with a peak effect at 20 to 60 minutes. The effect of mannitol on ICP lasts 1.5 to 6 hours, depending on the clinical condition [48]. Mannitol usually is given as a bolus of 0.25 g/kg to 1 g/kg body weight; when urgent reduction of ICP is needed, an initial dose of 1 g/kg body weight should be given. Arterial hypotension (systolic blood pressure < 90 mm Hg) should be avoided. Two prospective clinical trials, one in patients who had subdural hematoma and the other in patients who had herniated from diffuse brain swelling, have suggested that a higher dose of mannitol (1.4 g/kg) may give significantly better results in these extremely critical

situations than lower doses of mannitol [49,50]. When long-term reduction of ICP is needed, 0.25 to 0.5 g/kg can be repeated every 2 to 6 hours. Attention should be paid to replacing fluid that is lost because of mannitol-induced diuresis, or intravascular volume depletion will result.

Mannitol has rheologic and osmotic effects. Infusion of mannitol is immediately followed by an expansion of plasma volume and a reduction in hematocrit and blood viscosity, which may increase CBF and, on balance, increase oxygen delivery to the brain. These rheologic effects of mannitol depend on the status of pressure autoregulation [51]. In patients who have intact pressure autoregulation, infusion of mannitol induces cerebral vasoconstriction, which maintains CBF constant, and the decrease in ICP is large. In patients who have no pressure autoregulation, infusion of mannitol increases CBF, and the decrease in ICP is less pronounced. Mannitol also may improve microcirculatory rheology [50] and has free radical scavenging effects.

The osmotic effect of mannitol increases serum tonicity, which draws edema fluid from cerebral parenchyma. This process takes 15 to 30 minutes, until gradients are established. Serum osmolarity seems to be optimal when increased to 300 to 320 mOsm and should be kept at less than 320 mOsm to avoid the side effects of therapy, such as hypovolemia, hyperosmolarity, and renal failure. Mannitol opens the blood–brain barrier, and mannitol that has crossed the blood–brain barrier may draw fluid into the central nervous system, which can aggravate vasogenic edema. For this reason, when it is time to stop mannitol, it should be tapered to prevent a rebound in cerebral edema and ICP. The adverse effects of mannitol are most likely when mannitol is present in the circulation for extended periods, such as in slow or continuous infusions or with repeated administration of higher than necessary doses.

Hypertonic saline, given in concentrations ranging from 3% to 23.4%, also creates an osmotic force to draw water from the interstitial space of the brain parenchyma into the intravascular compartment in the presence of an intact blood–brain barrier, reducing intracranial volume and ICP. In some studies, hypertonic saline has been more effective than mannitol in reducing ICP [52,53]. Hypertonic saline has a clear advantage over mannitol in hypovolemic and hypotensive patients. Mannitol is contraindicated in hypovolemic patients because of the diuretic effects, whereas hypertonic saline augments intravascular volume and may increase blood pressure, in addition to decreasing ICP. Hypertonic saline was not associated with improved neurologic outcomes, however, when given as a prehospital bolus to hypotensive patients who had severe TBI [54]. Adverse effects of hypertonic saline administration include hematologic and electrolyte abnormalities (such as bleeding secondary to decreased platelet aggregation and prolonged coagulation times), hypokalemia, and hyperchloremic acidosis [55]. Hyponatremia should be excluded before administering hypertonic saline, to reduce the risk for central pontine myelinolysis [56].

Hyperventilation

Hyperventilation decreases Pa_{CO_2}, which can induce constriction of cerebral arteries by alkalinizing the CSF. The resulting reduction in cerebral blood volume decreases ICP. Hyperventilation has limited use in the management of intracranial hypertension, however, because this effect on ICP is time limited, and because hyperventilation may produce a decrease in CBF sufficient to induce ischemia.

The vasoconstrictive effect on cerebral arterioles lasts only 11 to 20 hours because the pH of the CSF rapidly equilibrates to the new Pa_{CO_2} level. As the CSF pH equilibrates, the cerebral arterioles redilate, possibly to a larger caliber than at baseline, and the initial reduction in cerebral blood volume comes at the cost of a possible rebound phase of increased ICP [57,58]. For this reason, the most effective use of hyperventilation is acutely, to allow time for other, more definitive treatments to be put into action. When hypocarbia is induced and maintained for several hours, it should be reversed slowly, over several days, to minimize this rebound hyperemia [59].

Hyperventilation decreases CBF, but whether this reduction in flow is sufficient to induce ischemia in the injured brain is controversial. One prospective study showed that acutely reducing Pa_{CO_2} from an average of 36 mm Hg to 29 mm Hg reduced global CBF and significantly increased the volume of brain that was markedly hypoperfused despite improvements in ICP and CPP [60]. Diringer and coworkers [61] showed similar changes in CBF with moderate hyperventilation, but did not observe any changes in regional $CMRO_2$, even when CBF was reduced to less than 10 mL/100 g/min in injured brain tissue, suggesting that energy failure associated with cerebral ischemia was not occurring.

Although hyperventilation-induced ischemia has not been clearly shown, routine chronic hyperventilation (to Pa_{CO_2} of 20–25 mm Hg) had a detrimental effect on outcome in one randomized clinical trial [59]. The investigators of this study recommended using hyperventilation only in patients who have intracranial hypertension, rather than as a routine in all head-injured patients. This view is reinforced in TBI guidelines.

Barbiturate coma

Barbiturate coma should only be considered for patients who have refractory intracranial hypertension because of the serious complications associated with high-dose barbiturates, and because the neurologic examination becomes unavailable for several days [62]. Pentobarbital is given in a loading dose of 10 mg/kg body weight followed by 5 mg/kg body weight each hour for three doses. The maintenance dose is 1 to 2 mg/kg/h, titrated to a serum level of 30 to 50 μg/mL or until the electroencephalogram shows a burst suppression pattern. Although routine use of barbiturates in unselected patients has not been consistently effective in reducing morbidity or mortality after severe head injury [63,64], a randomized multicenter trial showed

that instituting barbiturate coma in patients who had refractory intracranial hypertension resulted in a twofold greater chance of controlling the ICP [65].

The mechanism of ICP reduction by barbiturates is unclear but it likely reflects a coupled reduction in CBF and $CMRO_2$, with an immediate effect on ICP. Studies by Messeter and colleagues [66,67] have suggested that the reduction in ICP with barbiturates is closely tied to the retention of carbon dioxide reactivity by the brain. Complications occurring during treatment with barbiturate coma include hypotension in 58% of patients, hypokalemia in 82%, respiratory complications in 76%, infections in 55%, hepatic dysfunction in 87%, and renal dysfunction in 47% [68]. Hypotension caused by pentobarbital should be treated first with volume replacement and then with vasopressors, if necessary. Experimental studies suggest that for the treatment of hypotension associated with barbiturate coma, volume resuscitation may be better than dopamine [69] because dopamine infusion increased cerebral metabolic requirements and partially offset the beneficial effects of barbiturates on $CMRO_2$.

Hypothermia

Although a multicenter randomized clinical trial of moderate hypothermia in severe TBI did not show a beneficial effect on neurologic outcome, fewer patients randomized to moderate hypothermia had intracranial hypertension [70]. A pilot randomized clinical trial of hypothermia in children who had TBI produced similar findings (ie, no improvement in neurologic outcome, but a reduction in ICP during the hypothermia treatment) [71]. Although routine induction of hypothermia is not indicated at present, hypothermia may be an effective adjunctive treatment of increased ICP refractory to other medical management.

Steroids

Steroids are commonly used for primary and metastatic brain tumors to decrease vasogenic cerebral edema. Focal neurologic signs and decreased mental status owing to surrounding edema typically begin to improve within hours [72]. Increased ICP, when present, decreases over the following 2 to 5 days, in some cases to normal. The most commonly used regimen is intravenous dexamethasone, 4 mg every 6 hours. For other neurosurgical disorders, such as TBI or spontaneous intracerebral hemorrhage, steroids have not been shown to have a benefit [73,74] and in some studies have had a detrimental effect [75,76].

The CRASH trial [75] is a recently completed, large ($>10,000$ patients enrolled), placebo-controlled randomized clinical trial of methylprednisolone for 48 hours in patients who have TBI. Administration of methylprednisolone resulted in a significant increase in the risk for death, from 22.3% to 25.7% (relative risk 1.15, 95% CI 1.07–1.24). This trial confirmed

previous studies and guidelines that routine administration of steroids is not indicated for patients who have TBI.

Surgical interventions

Resection of mass lesions

Intracranial masses producing elevated ICP should be removed when possible. Acute epidural and subdural hematomas are a hyperacute surgical emergency, especially epidural hematoma because the bleeding is under arterial pressure. Brain abscess must be drained, and pneumocephalus must be evacuated if it is under sufficient tension to increase ICP. Surgical management of spontaneous intracerebral bleeding is controversial [77].

Cerebrospinal fluid drainage

CSF drainage lowers ICP immediately by reducing intracranial volume, and more long term by allowing edema fluid to drain into the ventricular system. Drainage of even a small volume of CSF can lower ICP significantly, especially when intracranial compliance is reduced by injury. This modality can be an important adjunctive therapy for lowering ICP. However, if the brain is diffusely swollen, the ventricles may collapse, and this modality then has limited usefulness.

Decompressive craniectomy

The surgical removal of part of the calvaria to create a window in the cranial vault is the most radical intervention for intracranial hypertension, negating the Monro-Kellie doctrine of fixed intracranial volume and allowing for herniation of swollen brain through the bone window to relieve pressure. Decompressive craniectomy has been used to treat uncontrolled intracranial hypertension of various origins, including cerebral infarction [78], trauma, subarachnoid hemorrhage, and spontaneous hemorrhage. Patient selection, timing of operation, type of surgery, and severity of clinical and radiologic brain injury are all factors that determine the outcome of this procedure.

Sahuquillo and Arikan [79] reviewed the evidence in the literature of studies evaluating the effectiveness of decompressive craniectomy after TBI. They found only one small randomized clinical trial in 27 children who had TBI [80]. This trial found a reduced risk ratio for death of 0.54 (95% CI 0.17–1.72), and a risk ratio of 0.54 for death, vegetative status, or severe disability 6 to 12 months after injury (95% CI 0.29–1.07). All the available studies in adults are either case series or cohorts with historical controls. These reports suggest that decompressive craniectomy effectively reduces ICP in most (85%) patients who have intracranial hypertension refractory to conventional medical treatment [81,82]. Brain oxygenation measured by tissue Po_2, and blood flow estimated by middle cerebral artery flow

velocity, are also usually improved after decompressive craniectomy [83,84]. Reported complications include hydrocephalus, hemorrhagic swelling ipsilateral to the craniectomy site, and subdural hygroma [81]. A case report of paradoxical herniation has also been reported after a lumbar puncture in a patient who had a decompressive craniectomy [85].

Results from randomized trials to confirm or refute the effectiveness of decompressive craniectomy in adults are limited. Reports suggest, however, that decompressive craniectomy may be a useful option when maximal medical treatment has failed to control ICP. Randomized controlled trials in TBI are ongoing (Rescue ICP [86] and DECRAN). In a pooled analysis of randomized trials in patients who had malignant MCA infarction, decompressive surgery undertaken within 48 hours of stroke was associated with reduced mortality and an increased proportion of patients who had a favorable functional outcome [87].

Summary

Effective treatment of intracranial hypertension involves meticulous avoidance of factors that precipitate or aggravate increased ICP. When ICP becomes elevated, it is important to rule out new mass lesions that should be surgically evacuated. Medical management of increased ICP should include sedation, drainage of CSF, and osmotherapy with either mannitol or hypertonic saline. For intracranial hypertension refractory to initial medical management, barbiturate coma, hypothermia, or decompressive craniectomy should be considered. Steroids are not indicated and may be harmful in the treatment of intracranial hypertension resulting from TBI.

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