



ICP Monitoring and Intracranial Hypertension: A case Report and Review of Literature

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KEYWORDS

a 15 month old, male child was referred to our centre with persistent seizures. He had fever since 15 days for which he was on oral medicine and after generalized seizure was admitted at Bhavnagar. He was investigated there and found to have bacterial meningitis. He had persistent seizure episode in spite of anticonvulsant and antibiotics in meningitic dose with steroids for 2 days. After 2 days of treatment he had persistent seizure and sensorium also worsen in form of irregular respiration and not responding to even painful stimuli. He was referred to our centre for further treatment.

On admission- child seizure present with intermittent tonic posturing, Febrile (102 F) with tachycardia (heart rate 189/min), Irregular respiration, and blood pressure was 92/40mmHg (mean blood pressure 57mmHg). Glass glow coma scale was 4/15 [E1 V1 M2], pupils – bilaterally mid-size sluggishly reacting to light. Pt was intubated by rapid sequence intubation (RSI), in view of poor sensorium and persistent seizures. Pt was loaded with fosphenytoin (30mg/kg) and phenobarbitone. Midazolam was given stat 0.2mg/kg followed by 0.1mg/kg/hr (1.6 µg/kg/min) and sodium valproate loaded (20mg/kg) followed by maintenance dose. IV antibiotics Meropenam and Vancomycin started in meningitic dose. Inj Mannitol given round the clock every 6 hourly. Midazolam infusion was gradually increased up to 8 µg/kg/min. Blood sugar and electrolytes checked. Hb was 7.0gm%, so given RBC 15ml/kg. CSF examination s/o 206mg/dl protein, 65mg/dl glucose, Total cell 680 , 85% polymorphs, 15% lymphocyte, 2-4 RBC/HPF.

After 36 hours of treatment patient had intermittent seizure episode. MRI done s/o changes of leptomeningitis with diffuse meningeal enhancement in cortical sulci and basal cistern. Restricted diffusion with hyper density in right fronto-temporo-parietal lobes and left frontal lobe suggest vasculitis with ischemic changes. Mild communicating hydrocephalus seen.

In spite of all measures patient had seizure and neurological status not improved so we started intracranial pressure monitoring in this patient. We did ventriculostomy through right parietal approach. Intra ventricular drain was placed at anterior horn of right lateral ventricle, other end was connected to monitor transducer and arrangement made to drain measured amount of CSF in close container. Zeroing of machine was done at level of tragus of right ear of patient.

First measurement of intra cranial pressure was 62 mmHg and at that time mean blood pressure was 60mmHg. Then we drained 15ml of CSF and ICP reduced to 35mmHg. After 3 hours we again drained 10 ml of CSF and ICP was kept 20mmHg. For subsequent days we drained CSF about 2-3 times/day about 10ml each time and we kept ICP below 20mmHg. Child improved in form of seizure stopped and neu-

rological status and sensorium improved.

We taper midazolam infusion gradually to 1 µg/kg/min. Child was extubated on 6th day uneventfully. Antibiotics completed for 21 days and patient was on oral AED on discharge. At follow up after 1 month child has completely recovered neurologically and was walking without support.

Discussion Intracranial Hypertension

The skull and dura form a relatively fixed space. Intracranial pressure is determined by the volume of its contents—brain, blood, and cerebrospinal fluid (CSF). An increase in the volume of one of these components must result in a decrease in the others, a principle known as the Monroe-Kellie doctrine [1]. If the volume of 1 of these components continues to increase, ICP will begin to increase. Out of many of the treatments for intracranial hypertension attempt to reduce the volume of 1 of these components, thus reducing ICP.

Cerebral perfusion pressure (CPP) is defined as the difference between ICP and mean arterial blood pressure. Reduced CPP is associated with hypoxic/ischemic injury

regardless of the ICP. Cerebral perfusion pressure is therefore an important parameter to monitor and maintain when treating increased ICP.

Clinical signs and symptoms of increased ICP vary depending on etiology. Common symptoms include headache, vomiting, and mental status changes. Papilledema is a common sign of increased ICP regardless of etiology.

The normal range for ICP varies with age. Values for pediatric patients are not as well established. Normal values are less than 10 to 15mmHg 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 sub atmospheric in newborns [2]. Normal adult ICP is defined as 5 to 15 mm Hg (7.5–20 cm H₂O). 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 20mmHg [3]. In most circumstances, ICP values of greater than 20 to 25 mm Hg require treatment. Sustained ICP values of greater than 40 mm Hg indicates 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:

$$CPP = MAP - ICP$$

where MAP = (1/3 systolic BP) + (2/3 diastolic BP)

As a result, CPP can be reduced by an increase in ICP, a de-

crease in blood pressure, or a combination of both factors. Through the normal regulatory process called pressure auto regulation, 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 auto regulate may be absent or impaired and, even with a normal CPP, CBF can passively follow changes in CPP.

When CPP is within the normal auto regulatory range (50–150 mm Hg), this ability of the brain to pressure auto regulate also affects the response of ICP to a change in CPP [4-6]. When pressure auto regulation is intact, decreasing CPP results in vasodilatation of cerebral vessels, which allows CBF to remain unchanged. This vasodilatation 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 auto regulation is impaired or absent, ICP decreases and increases with changes in CPP.

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, pseudo tumor cerebri, pneumocephalus, abscess, cyst)
Extra cranial (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, leads intoxication)
Others (eg, high-altitude cerebral edema, hepatic failure)
Postoperative
Mass lesion (hematoma)
Edema
Increased cerebral blood volume (vasodilatation)
Disturbance of CSF

Neurological intensive care monitoring

Intracranial hypertension is an important cause of secondary injury in patients who have acute neurological 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 PO₂, 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 [7].

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 [8].

Types of monitors

The ventriculostomy catheter is the preferred device for monitoring ICP and the standard against which all newer monitors are compared [9]. 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, neurological 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 micro sensor 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 [10]. The main advantage 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 [11]. Subdural and epidural monitors for ICP measurements are less accurate, when compared with ventriculostomy or parenchymal monitors.

ICP monitoring is continued for as long as treatment of intracranial hypertension is required, typically 3 to 5 days.

Indications for intracranial pressure monitoring

When 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

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 [12]. 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 [13]. 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 [14]. Use of antibiotic-coated ventriculostomy catheters has been shown to reduce the risk for infection from 9.4% to 1.3% [15].

Other complications of ventriculostomy catheters are hemorrhage (with an overall incidence of 1.4%), malfunction, obstruction, and malposition.

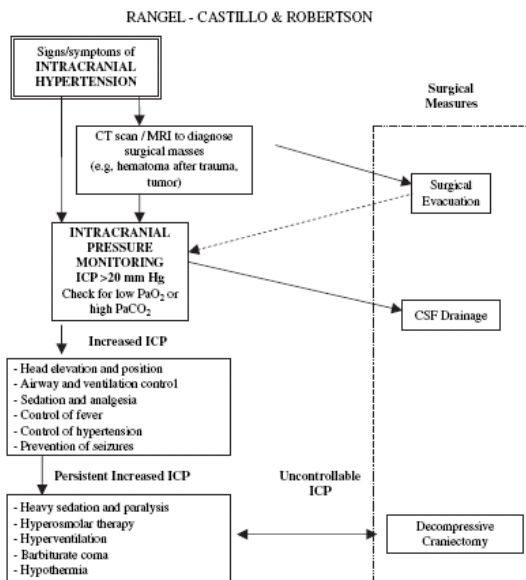
General care to minimize intracranial hypertension

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,
- Seizures.

Overall approach to the management of intracranial hypertension



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 [16]. A commonly used regimen is morphine and lorazepam for analgesia/sedation and atracurium or vecuronium as a muscle relaxant, with the dose titrated by twitch response to stimulation. A disadvantage of this therapy is that the neurological examination cannot be monitored closely; however, the sedatives and muscle relaxants can be interrupted once a day, usually before morning rounds, to allow neurological 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 [17]. 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 [18].

Hyperosmolar therapy

Mannitol is the most commonly used hyperosmolar agent for the treatment of intracranial hypertension. 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 [19]. 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. In arterial hypotension (systolic blood pressure < 90 mm Hg) it 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 [20,21]. 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 auto regulation [22]. In patients who have intact pressure auto regulation, infusion of mannitol induces cerebral vasoconstriction, which maintains CBF constant, and the decrease in ICP is large. In patients who have no pressure auto regulation, infusion of mannitol

increases CBF, and the decrease in ICP is less pronounced. Mannitol also may improve microcirculatory rheology [21] 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 osmolality 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, hyperosmolality, 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 [23, 24].

Hypertonic saline has a clear advantage over mannitol in hy-

povolemic 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 neurological outcomes, however, when given as a prehospital bolus to hypotensive patients who had severe TBI [25]. 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 [26]. Hyponatremia should be excluded before administering hypertonic saline, to reduce the risk for central pontine myelinolysis [27].

Hyperventilation

Hyperventilation decreases PaCO₂, which can induce constriction of cerebral arteries by alkalizing 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.

Although hyperventilation-induced ischemia has not been clearly shown, routine chronic hyperventilation (to PaCO₂ of 20–25 mm Hg) had a detrimental effect on outcome in one randomized clinical trial [28]. 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.

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 neurological examination becomes unavailable for several days [29]. 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 mg/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 [30, 31], 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 [32].

Hypothermia

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. A pilot randomized clinical trial of hypothermia in children who had TBI showed no improvement in neurological outcome, but a reduction in ICP during the hypothermia treatment [33].

Steroids

The CRASH trial [34] 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. Surgical management of spontaneous intracerebral bleeding is controversial [35].

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 [36], trauma, subarachnoid hemorrhage, and spontaneous hemorrhage. Patient selection, timing of operation, type of surgery, and severity of clinical and radiological brain injury are all factors that determine the outcome of this procedure.

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.

1. Placement Of catheter through right parietal route and with 3 way valve attached to pressure transducer for ICP measurement and provision to drain measured amount of CSF also made.



2. Monitor display showing mean blood pressure, ICP, ETCO₂, HR, SPO₂



3. Provision to drain measured amount of CSF



References

- Ropper AH, Brown RH. Adams and Victor's principles of neurology. 8th ed. New York, NY: McGraw-Hill; 2005. p. 529-45.
- Welch K. The intracranial pressure in infants. *J Neurosurg* 1980; 52:693-9.
- Andrews BT, Chiles BW III, Oslan WL, et al. The effect of intracerebral hematoma location on the risk of brain stem compression and on clinical outcome. *J Neurosurg* 1988; 69:518-22.
- Hlatky R, Valadka AB, Robertson CS. Intracranial pressure response to induced hypertension: role of dynamic pressure auto regulation. *Neurosurgery* 2005; 57:917-23.
- Rosner MJ, Coley IB. Cerebral perfusion pressure, intracranial pressure, and head elevation. *J Neurosurg* 1986; 65:636-41.
- Gobiet W, Grote W, Bock WJ. The relation between intracranial pressure, mean arterial pressure and cerebral blood flow in patients with severe head injury. *Acta Neurochir (Wien)* 1975; 32:13-24.
- Selhorst JB, Gudeman SK, Butterworth JF, et al. Papilledema after acute head injury. *Neurosurgery* 1985; 16:357-63.
- Kishore PR, LipperMH, Becker DP, et al. Significance of CT in head injury: correlation with intracranial pressure. *AJR Am J Roentgenol* 1981; 137:829-33.
- Adelson PD, Bratton SL, Carney NA, et al. Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents: chapter 7. Intracranial pressure monitoring technology. *Pediatr Crit Care Med* 2003; 4:S28-30.
- Gopinath SP, Robertson CS, Contant CF, et al. Clinical evaluation of a miniature strain gauge transducer for monitoring intracranial pressure. *Neurosurgery* 1995; 36:1137-40.
- Czosnyka M, Czosnyka Z, Pickard JD. Laboratory testing of three intracranial pressure micro transducers: technical report. *Neurosurgery* 1996; 38:219-24.
- Mayhall CG, Archer NH, Lamb VA, et al. Ventriculostomy-related infections: a prospective epidemiologic study. *N Engl J Med* 1984; 310:553-9.
- Holloway KL, Barnes T, Choi S, et al. Ventriculostomy infections: the effect of monitoring duration and catheter exchange in 584 patients. *J Neurosurg* 1996; 85:419-24.
- Park P, Garton HJL, Kocan MJ, et al. Risk of infection with prolonged ventricular catheterization. *Neurosurgery* 2004; 55:594-601.
- Zabramski JM, Whiting D, Darouiche RO, et al. Efficacy of antimicrobial impregnated external ventricular drain catheters: a prospective, randomized, controlled trial. *J Neurosurg* 2003; 98:725-30.
- Schramm WM, Papousek A, Michalek-Sauberer A, et al. The cerebral and cardiovascular effects of cisatracurium and atracurium in neurosurgical patients. *Anesth Analg* 1998; 86: 123-7.
- Nates JL, Cooper DJ, Day B, et al. Acute weakness syndromes in critically ill patients: a reappraisal. *Anaesth Intensive Care* 1997; 25:502-13.
- Prielipp RC, Coursin DB, Scuderi PE, et al. Comparison of the infusion requirements and recovery profiles of vacoronium and cisatracurium 51W89 in intensive care unit patients. *Anesth Analg* 1995; 81:3-12.
- Knapp JM. Hyperosmolar therapy in the treatment of severe head injury in children: mannitol and hypertonic saline. *AACN Clin Issues* 2005; 16:199-211.
- Cruz J, Minoja G, Okuchi K, et al. Successful use of the new high-dose mannitol treatment in patients with Glasgow Coma Scale scores of 3 and bilateral abnormal pupillary widening: a randomized trial. *J Neurosurg* 2004; 100:376-83.
- Cruz J, Minoja G, Okuchi K. Improving clinical outcomes from acute subdural hematomas with the emergency preoperative administration of high doses of mannitol: a randomized trial. *Neurosurgery* 2001; 49:864-71.
- Muizelaar JP, Lutz HA, Becker DP. Effect of mannitol on ICP and CBF and correlation with pressure auto regulation in severely head-injured patients. *J Neurosurg* 1984; 61:700-6.
- Battison C, Andrews PJ, Graham C, et al. Randomized, controlled trial on the effect of a 20% mannitol solution and a 7.5% saline/6% dextran solution on increased intracranial pressure after brain injury. *Crit Care Med* 2005; 33:196-202.
- Vialet R, Albanese J, Thomachot L, et al. Isovolume hypertonic solutes (sodium chloride or mannitol) in the treatment of refractory posttraumatic intracranial hypertension: 2 mL/kg 7.5% saline is more effective than 2 mL/kg 20% mannitol. *Crit Care Med* 2003; 31:1683-7.
- Cooper DJ, Myles PS, McDermott FT, et al. Prehospital hypertonic saline resuscitation of patients with hypotension and severe traumatic brain injury: a randomized controlled trial. *J Am Med Assoc* 2004; 291:1350-7.
- Doyle JA, Davis DP, Hoyt DB. The use of hypertonic saline in the treatment of traumatic brain injury. *J Trauma* 2001; 50:367-83.
- Bratton SL, Chestnut RM, Ghajjar J, et al. Hyperosmolar therapy. *J Neurotrauma* 2007; 24(Suppl 1):S14-20.
- Muizelaar JP, van der Poel HG, Li ZC, et al. Pial arteriolar vessel diameter and CO₂ reactivity during prolonged hyperventilation in the rabbit. *J Neurosurg* 1988; 69:923-7.
- Bader MK, Arbour R, Palmer S. Refractory increased intracranial pressure in severe traumatic brain injury: barbiturate coma and bispectral index monitoring. *AACN Clin Issues* 2005; 16:526-41.
- Schwartz ML, Tator CH, Rowed DW, et al. The University of Toronto Head Injury Treatment Study: a prospective, randomized comparison of pentobarbital and mannitol. *Can J Neurol Sci* 1984; 11:434-40.
- Ward JD, Becker DP, Miller JD, et al. Failure of prophylactic barbiturate coma in the treatment of severe head injury. *J Neurosurg* 1985; 62:383-8.
- Eisenberg HM, Frankowski RF, Contant CF, et al. High-dose barbiturate control of elevated intracranial pressure in patients with severe head injury. *J Neurosurg* 1988; 69: 15-23.
- Adelson PD, Ragheb J, Kanev P, et al. Phase II clinical trial of moderate hypothermia after severe traumatic brain injury in children. *Neurosurgery* 2005; 56:740-54.
- Edwards P, Arango M, Balica L, et al. Final results of MRCCRASH, a randomised placebo controlled trial of intravenous corticosteroid in adults with head injury outcomes at 6 months. *Lancet* 2005; 365:1957-9.
- Marchuk G, Kaufmann AM. Spontaneous supratentorial intracerebral hemorrhage: the role of surgical management. *Can J Neurol Sci* 2005; 32(Suppl 2):S22-30.
- Cheung A, Telaghani CK, Wang J, et al. Neurological recovery after decompressive craniectomy for massive ischemic stroke. *Neurocrit Care* 2005; 3:216-23.