J Anesth (2002) 16:229–237

Journal of
Anesthesia

Cerebral resuscitation: role of osmotherapy

Izumi Harukuni[1], Jeffrey R. Kirsch[1,2], and Anish Bhardwaj[1,2]

[1]Department of Anesthesiology/Critical Care Medicine, Neurosciences Critical Care Division, Meyer 8-140, Johns Hopkins Hospital, 600 N Wolfe Street Baltimore, MD 21287, USA
[2]Department of Neurology, Johns Hopkins University School of Medicine Baltimore, Maryland, USA

Key words Brain · Cerebral · Resuscitation · Intracranial pressure · Osmotherapy

Introduction

Primary brain injury can result from a variety of causes, including trauma, focal or global cerebral ischemia, intraparenchymal or subarachnoid hemorrhage, infection, or toxic-metabolic derangements. Secondary neuronal injury may ensue from a variety of factors, including cerebral edema that may accompany elevated intracranial pressure (ICP), and compromise cerebral blood flow (CBF). The use of osmotic agents constitutes the cornerstone of medical therapy in acute brain resuscitation from cerebral edema and elevated ICP in all brain injury paradigms. While mannitol is the osmotic agent of choice, hypertonic saline (HS) solutions have received renewed attention as agents that hold promise in the future. This article reviews and highlights the pathophysiological principles of osmotherapy and the mechanisms of action of osmotic agents, and elaborates on their use in patients with acute brain injury.

Fundamental principles of acute brain resuscitation

Cerebral edema and elevated ICP are frequently encountered in clinical practice in patients with brain injury of diverse etiologies [1–6]. Cerebral edema, defined as increased brain water content, may or may not translate into elevated ICP [1,2,5,6]. Global increases in ICP may compromise cerebral perfusion pressure (CPP; mean arterial blood pressure [MAP] − ICP) and CBF and may lead to cerebral ischemia and irreversible brain injury [5–7]. However, focal cerebral edema can act as a mass that may lead to lethal intracranial compartmental shifts, causing compression of vital brain structures that are characterized by a constellation of symptoms and signs (herniation syndromes) [1,2,5–7] (Table 1). Thus, herniation syndromes can exist in the face of normal global ICP. Serial neurologic examinations focusing on the constellation of signs that help prompt recognition of these syndromes is paramount in instituting therapeutic interventions in a timely fashion [8]. Traditionally, cerebral edema has been classified as: (a) cytotoxic, as a consequence of cellular energy failure (Na^+-K^+ pump disruption) (b) vasogenic, secondary to increased vascular permeability to plasma components because of dysfunction of glial foot processes, (c) hydrocephalic edema, secondary to the obstruction of cerebrospinal fluid (CSF) pathways leading to the periventricular extravasation of CSF, (d) hydrostatic, because of elevated systemic blood pressure, and (e) osmotic, because of plasma hypo-osmolality [5,6,9] (Table 2).

From a therapeutic perspective, there is considerable overlap in the management of cerebral edema with or without elevated ICP [1,2,5,6] (Table 3). *General measures* for treatment focus on preventing any increases in blood pressure and ICP (e.g., avoidance of shivering, agitation, and excessive stimulation, and the maintaining of adequate analgesia) and assuring adequate cerebral venous drainage (mid-head positioning and elevation, euvolemia). *Specific therapies* for elevated ICP include controlled hyperventilation, the use of osmotic agents and diuretics, controlled cerebrospinal fluid (CSF) drainage, and cerebral metabolic suppression with pharmacological coma (barbiturates and propofol) [1,2,5,6]. More recently, hypothermia, with or without decompressive hemicraniectomy, has received attention as "rescue" therapy for certain brain injuries [10–12], but evidence for the efficacy of these modalities remains largely anecdotal and unproven.

Address correspondence to: A. Bhardwaj
Received: March 15, 2002 / Accepted: April 2, 2002

Table 1. Various types of herniation syndromes. Early recognition is paramount in instituting resuscitative therapies

Syndrome	Clinical manifestations
Subfalcian or cingulate	Usually a neuroradiological diagnosis Cingulate gyrus herniates under the falx cerebrii May cause compression of ipsilateral ACA Contralateral lower extremity paresis
Central tentorial	Downward displacement of one or both cerebral hemispheres causing compression of diencephalon and midbrain through tentorial notch Usually due to centrally located masses Impaired consciousness and eye movements; elevated ICP Bilateral decorticate or decerebrate posturing
Lateral transtentorial (uncal)	Most common; usually due to laterally located masses such as tumors and hematomas Medial temoral lobe, uncus, and hippocampal gyrus herniates through the tentorial incisura Compression of occumotor nerve, midbrain, and PCA; depressed level of consciousness; ipsilateral papillary dilatation and contralateral hemiparesis Decerebrate posturing, central neurogenic hyperventilation Elevated ICP
Tonsillar	Herniation of cerebellar tonsils through foramen magnum leading to medullary compression Most frequently due to masses in the posterior fossa Precipitous changes in BP and heart rate; small pupils, ataxic breathing, disturbance of conjugate gaze and quadriparesis
External	Due to penetrating injuries to the skull, e.g., gunshot wound or skull fractures Loss of CSF and brain tissue ICP may not be elevated due to dural opening

ACA, Anterior cerebral artery; PCA, posterior cerebral artery; ICP, intracranial pressure; BP, blood pressure; CSF, cerebrospinal fluid

Table 2. Classification of cerebral edema

Classification	Location	Site	Integrity of BBB	Postulated mechanism	Disease
Cytotoxic	Intracellular	White and gray	Intact	Cellular energy failure	Anoxia Water intoxication Reye's syndrome
Vasogenic	Extracellular	White matter	Disrupted	Increased vascular permeability to plasma components	Brain tumor Trauma Brain abscess Meningitis ICH[a]
Ischemic	Intra- and extracellular	White and gray	Disrupted	Anoxia	Cerebral ischemia ICH[a]
Hydrostatic	Extracellular	White and gray	Disrupted	Increased BP	Hypertensive encephalopathy
Hydrocephalic	Extracellular	White	Intact	Perventricular extravasation	Hydrocephalus Pseudotumor cerebri[a]
Osmotic	Intra- and extracellular	White and gray	Intact	Plasma hypo-osmolality	Overhydration Hyponatremia SIADH

ICH, Intracerebral hemorrhage; SIADH, syndrome of inappropriate antidiuretic hormone secretion; BBB, blood brain barrier
Adapted from *Klatzo* [1], *Bingaman* and *Frank* [6] and *Bhardwaj* and *Ulatowski* [5]
[a] Uncertain diagnosis

Osmotherapy—historical perspective

Osmotherapy remains the cornerstone of medical therapy for cerebral resuscitation, irrespective of the etiology of cerebral edema with elevated ICP [5,6,13]. Through the years, a variety of osmotic agents have been utilized for this purpose in a variety of acute brain injury paradigms [5,13]. These agents include urea, mannitol, glycerol, sorbitol [13,14], and, more recently, HS solutions [5,14–16]. Weed and McKibben [17] were the first to describe the effects of administering intravenous osmotic agents on the brain. In 1919, they reported that the intravenous injection of a highly concentrated salt solution in patients resulted in subsequent inability to withdraw CSF from the lumbar cistern. This phenomenon was attributed to the collapse of the thecal sac

Table 3. Conventional therapies for cerebral resuscitation

General
Avoid shivering, agitation, or fever
Maintenance of euvolemic or slightly hypervolemic state
Pressors as needed to maintain CPP (usually > 70 mmHg)
Facilitate venous outflow (head elevation to 30° and midline position)
Specific
Controlled hyperventilation (Pa_{co_2}, 25–30 mmHg)
External CSF drainage
Osmotic therapy (osmotic agents, diuretics)
Metabolic suppression (barbiturates[a] propofol)
Blood brain barrier integrity (steroids)
Decompressive surgery
Hypothermia

Adapted from *Bhardwaj* and *Ulatowski* [5]
CPP, Cerebral perfusion pressure

around the lumbar subarachnoid space [13,17]. Subsequently, these observations were followed up with rigorous laboratory experiments with intravenous injections of 30% saline solution in anesthetized cats [13,17]. This intervention caused disappearance of the normal convexity of the brain soon after the injection, with maximum shrinkage of the brain occurring 15–30 min after the injection was completed. Conversely, marked brain swelling was observed after intravenous injections of distilled water [17]. This set of observations, detailing the effects of changes in plasma osmolality on brain parenchyma, has formed the basis of osmotherapy [13,17].

The first agent to be utilized formally as an osmotic agent was concentrated urea [18]. Interest in the use of concentrated human plasma proteins to raise oncotic pressure as a means of alleviating elevated ICP was dampened by the high cost of preparation and the potential for allergic reactions [13]. Mannitol, a simple alcohol derivative of the sugar mannose, came into clinical use in the 1960s. The popularity of mannitol resulted from its ease of preparation, stability in solution, and relative nontoxicity, and because it caused less vein irritation than that observed with urea.

Alternative theories of mechanisms for the beneficial effects of osmotic agents in the treatment of elevated ICP have emerged over the years [13]. It has been hypothesized that osmotic agents have dynamic effects on blood and CSF compartments of the intracranial vault. Mannitol, for example, has significant nonosmotic effects, including the enhancement of CBF, due to its antiviscosity effects by decreasing red cell volume, rigidity, and cohesiveness [13,19–26]. Mannitol has also been shown to possess neuroprotective properties by acting as a scavenger of oxygen-free radicals in the cerebral microvessels after trauma and glucose and oxygen deprivation [13].

Glycerol, an osmotic agent that is more commonly used in continental Europe (out of tradition), is naturally occurring in mammalian tissues [13]. It can rapidly decrease ICP when given orally, without significant gastrointestinal side effects, but may produce hemolysis when given rapidly by the intravenous route [13,27]. The use of glycerol in the United States has become almost negligible in patients with acute brain injury.

Despite their obvious therapeutic value, there was little interest in the clinical use of HS solutions until the early 1980s, when these solutions were utilized for small-volume resuscitation in patients with hemorrhagic shock [15]. These investigations demonstrated that the prehospital restoration of intravascular volume reduced the morbidity and mortality associated with massive hemorrhage [15]. In these studies, physiological parameters such as systemic blood pressure (BP), cardiac index, and tissue perfusion were improved by the use of small volumes of HS solutions. Subsequently, investigators studied the cerebral effects of these solutions in well-controlled laboratory studies in appropriate animal models that provided evidence for their potential use in patients with acute brain injury (see below).

Therapeutic rationale and goals of osmotherapy in cerebral resuscitation

In normal individuals, the serum osmolality (270–290 $mOsm \cdot l^{-1}$) is relatively constant from day to day and the serum sodium (Na^+) concentration is an estimate of body water osmolality [5]. Under ideal circumstances, serum osmolality can be calculated from the formula:

$$\text{Serum osmolality } (mOsm \cdot l^{-1}) = 2[Na^+ + K^+(mEq \cdot l^{-1})] + \text{plasma glucose } (mg \cdot dl^{-1})]/18 + [\text{blood urea nitrogen; BUN } (mg \cdot dl^{-1})]/2.8$$

However, in clinical medicine, particularly when providing care for critically ill patients, it is important to correlate the calculated osmolality to the osmolality measured with an osmometer to assess the degree by which other plasma constituents are contributing to total osmolality. Because urea is freely diffusible across cell membranes, blood urea nitrogen (BUN) is less important in maintaining an osmolar gradient between the intravascular compartment and the brain. Thus, serum sodium and plasma glucose are the key elements in altering serum osmolality. Osmotic agents exert their beneficial effects primarily by establishing an osmotic gradient between the intravascular space and the brain [5,13,15]. Such gradients provide a driving force to cause egress of water from the extracellular (and possibly intracellular) spaces of the brain into the capillaries, thereby decreasing the intracranial volume (comprised

of brain, 80%; blood, 10%; and CSF, 10%) and improving intracranial compliance [1,2,5].

The goal of osmotherapy for cerebral edema associated with brain injury is to maintain a euvolemic or a slightly hypervolemic state [5]. A hypo-osmolar state should always be avoided in any patient with an acute brain injury [2,5]. A serum osmolality in the range of 300–320 $mOsm \cdot l^{-1}$ is recommended for patients with acute brain injury who demonstrate poor intracranial compliance [2,5]. However, in an attempt to minimize intracranial pathology, serum osmolality of more than 320 $mOsm \cdot l^{-1}$ can be used with great caution, without apparent untoward side effects.

An ideal osmotic agent is one that produces a favorable osmotic gradient, is inert, nontoxic, has minimal systemic side effects, remains largely in the intravascular compartment, and is excluded from entry into the brain [5,13,15]. The specialized endothelium formed by tight junctions in the brain constitutes the blood brain barrier (BBB), and its ability to exclude a given compound has been quantified and expressed as a reflection coefficient (s) [5,13,15]. The value of this parameter varies between zero (freely permeable) and 1 (completely impermeable) [5,13,15]. Compounds with an s value approaching 1 are considered to be better osmotic agents because they are completely excluded by an intact BBB and, conversely, are less likely to exhibit "rebound" cerebral edema with elevations in ICP during withdrawal of therapy [5,13,15]. With mannitol ($s = 0.9$) use, the potential for cerebral edema and rebound elevations in ICP exists, as a result of the reversal of the osmotic gradient between the brain and the intravascular compartment in areas of disrupted BBB [13]. For example, mannitol appears in the CSF with levels of approximately 12% of the corresponding plasma concentration at 8 h after intravenous bolus administration [19], and rebound increases in ICP have been well documented with its use. Similarly, other older osmotic agents, glycerol ($s = 0.48$) and urea ($s = 0.59$), are less than ideal because their osmotic effects are transient, as they are only partly excluded by the intact BBB, and equilibration between the brain and intravascular compartment occurs rapidly [13,15]. Because sodium chloride has a reflection coefficient of 1.0, it is proposed to be a potentially more effective osmotic agent than mannitol [13,15].

Laboratory-based evidence

While there is a large body of literature demonstrating the beneficial effects of mannitol in animal models of acute brain injury, there are also emerging experimental data demonstrating HS as an effective osmotic agent in a variety of brain injury paradigms. For example, in neurologically intact rabbits, administration of hypertonic lactated Ringer's solution (osmolality of 480 $mOsm \cdot l^{-1}$) caused decreased ICP, decreased total brain water content, and increased CBF as compared with findings in rabbits treated with normal saline [28]. Subsequently, treatment with HS solutions in animal models of hemorrhagic shock, in the absence of brain injury, resulted in lower ICP, decreased brain water content, increased CBF, and improved oxygen delivery [29–31]. These findings were further confirmed in rats with acute and focal cryogenic brain injury, in which the administration of 23.4% saline produced both a greater and more sustained reduction in ICP (8-h observation) than mannitol administered in equimolar doses [32]. While HS was shown to worsen infarction volume when begun at the time of reperfusion after 2 h of transient focal ischemia in the rat [33], the mechanism of this detrimental effect was not due to impaired CBF. Little is known about the differential response of neurons and glia to HS solutions during the evolution of cerebral infarction. For example, in-vitro studies have demonstrated that hypertonic-hyperoncotic saline differentially affects healthy and glutamate-injured primary hippocampal neurons and astrocytes [34]. However, brain water content was decreased significantly when treatment was begun 24 h after the onset of focal ischemia and serum Na^+ was maintained at 145–155 $mEq \cdot l^{-1}$ [35]. Likewise, attenuation in brain edema produced with HS in this model was comparable to that achieved with large doses (2 $g \cdot kg^{-1}$ every 6 h) of bolus mannitol [35]. This supports the hypothesis that the beneficial osmotic effects of hypernatremia induced with HS are dependent on the timing of the initiation of therapy in relation to "maturation" of the lesion during cerebral ischemia. Continuous infusion of 3% HS also attenuated ICP and augmented CPP in a dog model of intracerebral hemorrhage, more so than conventional doses of intravenous bolus mannitol [36]. Recently, in a well-characterized model of experimental brain tumor, we have demonstrated that continuous intravenous infusion of 7.5% HS and maintenance of serum Na^+ at 145–155 $mEq \cdot l^{-1}$ for 48 h attenuates water content more effectively than high-dose bolus mannitol or furosemide [37]. Thus, these laboratory studies provide compelling evidence that HS is an effective osmotic agent in a variety of brain injury paradigms.

Data from clinical studies

Several prospective clinical studies, especially in the traumatic brain injury (TBI) paradigm, have demonstrated the beneficial effects of mannitol for the treatment of elevated ICP. In an uncontrolled series, Miller and Leach [26] demonstrated sustained decreases in

ICP, to 34% of pretreatment values, with bolus mannitol in patients with poor intracranial compliance. In a prospective series of patients with elevated ICP due to diverse intracranial pathologies, in a dose-escalating study, bolus mannitol decreased ICP, with a mean reduction of 52%, which was sustained for up to 88 min [38]. Marshall et al. [21], in an uncontrolled series (8 patients) of TBI, demonstrated that 0.25 g·kg^{-1} bolus mannitol was sufficient to cause reduction in elevated ICP. Other studies have demonstrated decreased ICP and enhanced CBF and CPP in patients with severe TBI treated with mannitol [22,23]. While many of these trials have centered on ICP effects and changes in physiological variables in the acute phase, there is a paucity of literature on long-term outcomes in these critically ill patients. Although the immediate response to mannitol was beneficial in a prospective randomized trial of 80 patients with TBI [24], long-term functional outcome was not affected in patients who responded with a lowering of ICP.

Based on the extension of laboratory-based research, a few human prospective studies, anecdotal case reports, and several uncontrolled case series have been reported using HS solutions in the treatment of cerebral edema and elevated ICP. Overall, the literature supports the use of HS as therapy to decrease ICP in patients after TBI and stroke, and to optimize intravascular fluid status in patients with subarachnoid hemorrhage-induced vasospasm. The first report to demonstrate the efficacy of HS in patients with TBI was by Worthley et al. [39]. This group described two patients with elevated ICP refractory to mannitol, who were treated successfully with a single bolus of 30% saline, after which ICP decreased and systemic perfusion improved. In another report, continuous infusion of 2.5% and 5.4% saline enhanced CPP and improved somatosensory evoked potentials in a patient with brain stem trauma [16]. Likewise, in an uncontrolled, nonrandomized study [40], there were reductions in ICP with a 7.5% HS solution after neurotrauma. In a double-blinded, crossover study, using 3% HS in children with TBI, ICP was reduced by approximately 5 mmHg for 2 h compared with ICP in patients requiring equal volumes of isotonic saline [41]. Because of the similar effects of mannitol and HS on ICP, Gemma et al. [42] performed a prospective randomized comparison of 2.5 ml·kg^{-1} of either 20% mannitol (1400 mOsm·kg^{-1}) or 7.5% saline (2560 mOsm·kg^{-1}) in patients undergoing elective supratentorial procedures ("surgical trauma"). Effects on CSF pressure, and the intraoperative clinical assessment of brain swelling, were similar in both treatment groups. However, the two solutions had different osmolalities, making the interpretation of results somewhat limited.

In an uncontrolled, nonrandomized, retrospective clinical series, we [43] have reported the beneficial effects (clinical and radiographic evidence of improvement in shift) following treatment with 3% hypertonic saline/acetate in patients with head trauma and postoperative cerebral edema, but not in patients with intracerebral hemorrhage or cerebral infarction. In a prospective randomized trial of 34 patients with TBI, Shackford et al. [44] have demonstrated that both HS and hypertonic lactated Ringer's solution were effective therapies in controlling ICP, although the admission Glasgow Coma Score was higher in patients treated with HS in their study. In a retrospective case series, we have demonstrated that 30-ml intravenous bolus administration of 23.4% saline (8008 mOsm·l^{-1}) reduced ICP and augmented CPP for up to 3 h in patients with intractable intracranial hypertension of diverse etiologies that were refractory to all conventional therapeutic modalities for cerebral resuscitation [45]. In a prospective, randomized, controlled study in children with severe TBI, Simma et al. [46] demonstrated lower ICP, higher CPP, fewer complications, and shorter intensive care unit (ICU) stay after HS treatment. We have reported, in a retrospective study, that the continuous infusion of HS (saline/acetate, 50:50 solution) in patients with TBI does not favorably impact on either the requirement for other interventions or inpatient mortality [47].

A number of clinical studies have supported the clinical utility of using HS in an attempt to minimize brain injury resulting from cerebral ischemia. We have demonstrated that HS solutions can be used safely, without untoward side effects, in patients with vasospasm and mild hyponatremia (presumably resulting from cerebral salt wasting), following aneurysmal subarachnoid hemorrhage [48]. In this subset of patients, HS augmented central venous pressures and CPP, both being desirable endpoints of therapy, in the setting of cerebral vasospasm. More recently, in a prospective randomized trial, HS with hydroxylethyl starch (for more prolonged action) has been shown to be more effective in lowering elevated ICP in patients with ischemic stroke and elevated ICP as compared with equiosmolar doses of mannitol [49]. Likewise, the intravenous bolus injection of 10% saline has been shown to be effective in lowering ICP in patients with ischemic stroke that failed to show such a response to conventional doses of mannitol [50].

Osmotherapy protocol for cerebral resuscitation

The conventional osmotic agent mannitol, when administered at a dose of 0.25 to 1.5 g·kg^{-1} by intravenous bolus injections, usually lowers ICP with maximal effects observed 20–40 min after its administration [13]. In the Neuroscience Critical Care unit at the Johns Hopkins Hospital, in patients with acute brain injury with poor intracranial compliance, instead of mannitol,

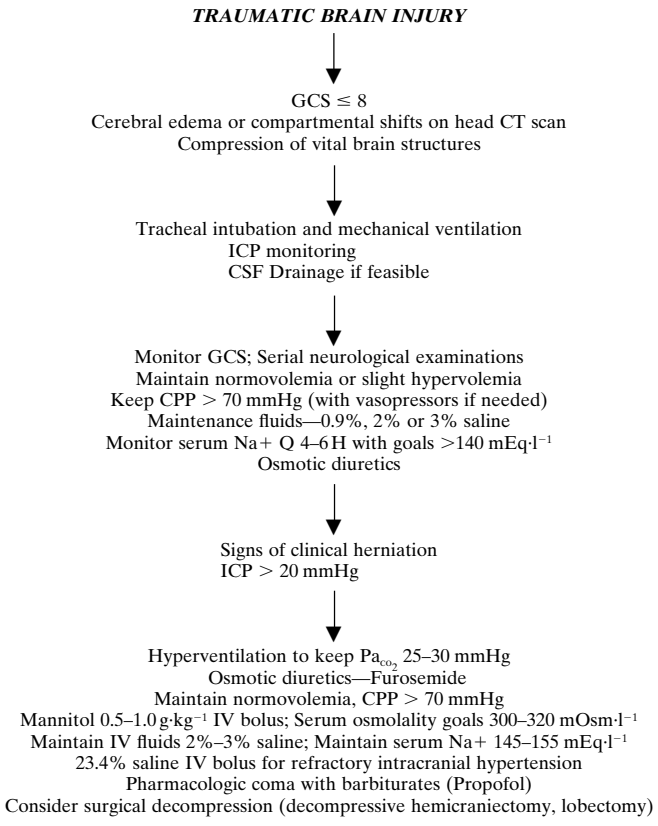

Fig. 1. Suggested algorithm for cerebral resuscitation after traumatic brain injury that can be extrapolated to other brain injury paradigms, *CT*, Computed tomography; *GCS*, Glasgous Coma Scale; *ICP*, intracranial pressure; *CSF*, cerebrospinal fluid; *CPP*, cerebral perfusion pressure. Adapted from Bhardwaj and Ulatowski [5], with permission

we use a 2% or 3% HS solution (Fig. 1). The HS is formulated to contain an equal amount of sodium chloride and sodium acetate (50:50) in order to avoid hyperchloremic acidosis associated with the administration of high-concentration sodium chloride solutions [15]. Potassium supplementation (40–60 mEq·l^{-1}) is added to the solution as needed. Intravenous infusions are started at a variable rate to achieve euvolemia or slight hypervolemia, ranging from 75 to 150 ml·h^{-1} (1–2 ml·kg^{-1}·h^{-1}) through a central venous catheter. A 250-ml bolus of HS is administered cautiously in selected patients if more aggressive and rapid resuscitation is warranted. Because HS may act as a diuretic, the assessment of urine output alone will not provide an accurate evaluation of intravascular fluid status. Therefore, normovolemic fluid status is maintained, as guided by central venous pressure or pulmonary artery wedge pressure (if available). The goal in using HS is to increase serum sodium concentration to a range of 145–155 mEq·l^{-1} (serum osmolality, approximately 300–320 mOsm·l^{-1}). This level of serum sodium is maintained for 48–72 h, or until patients demonstrate clinical improvement, develop systemic complications of therapy, or there is lack of response despite achieving this serum sodium goal. During withdrawal of therapy, special caution is emphasized to avoid rebound hyponatremia. Serum sodium and potassium are monitored every 4–6 h, both during the institution and the withdrawal of therapy [5]. Other serum electrolytes are monitored daily (with particular attention to calcium and magnesium). Chest radiographs are performed at least once every day to look for evidence of pulmonary edema from congestive heart failure, especially in elderly patients with poor cardiovascular reserve. Intravenous bolus injections (30 ml) of 23.4% saline have been utilized in patients with intracranial hypertension refractory to conventional ICP lowering therapies; repeated injections of 30-ml boluses of 23.4% saline may be given if needed to lower ICP. We have previously demonstrated that the administration of this osmotic load, to lower ICP and maintain CPP, may allow extra time for other diagnostic or therapeutic interventions (e.g., decompressive surgery) in critically ill patients [45]. However, safety data are limited with this degree of osmolar load, and it is advised that current therapy be guided by serum sodium in the 145- to 155-mEq·l^{-1} range.

Safety and potential complications

Therapeutic concerns with mannitol include significant systemic side effects, including hypotension, hemolysis, hyperkalemia, renal insufficiency, and pulmonary edema [5,13,15]. Our experience suggests that the side-effect profile of HS is much better in comparison to that of mannitol, but some theoretical complications are possible with HS therapy. These include myelinolysis, encephalopathy-confusion, lethargy, seizures, pulmonary edema, hypotension, coagulopathy, and phlebitis [5,15]. To date, there have been no "phase 1" trials for safety with HS solutions. Myelin injury is a well-known complication of rapid over-correction of preexisting hyponatremia. However, the threshold for myelin injury due to a change in serum sodium from a normonatremic to a sustained hypernatremic state is ill defined. In naïve-uninjured rats, induced hypernatremia (145–155 mEq·l^{-1}) with HS does not cause myelin injury (approximately 17 mEq·l^{-1}) [33], and a change of 35–40 mEq·l^{-1} is required to induce myelinolysis [51]. Other potential neurologic complications of rapid changes in sodium and plasma osmolality include symptoms and signs of encephalopathy (confusion, lethargy, seizures, and occasionally coma) [15]. Subdural hematomas or effusions may occur due to the shearing of bridging veins as a result of hyperosmolar contracture of the brain away from the dura. The risk

of rapid volume expansion is especially important in patients with poor cardiovascular reserve and a history of heart failure, neurogenic cardiac stun, or pulmonary edema. Anecdotal experiences suggest that, like mannitol, the bolus administration of HS can, paradoxically, induce transient acute hypotension. Rapid expansion of the plasma volume without concomitant potassium replacement could lead to hypokalemia and cardiac arrhythmias [15]. An increased plasma chloride concentration could result in metabolic (hyperchloremic) acidemia [15]. Hence, the use of HS solutions as a mixture of chloride/acetate (50:50) is recommended. Coagulopathy may result, with prolonged activated prothrombin and partial thromboplastin times and a decrease in platelet aggregation [15]. Whenever possible, slow infusion of HS solutions is recommended, because rapid changes in osmotic gradients in the serum may lead to hemolysis. Phlebitis may also occur if concentrated solutions are given through the peripheral route. Thus, a central venous route of administration is recommended when HS solutions are being used. Thus far, there are no reports of toxicity or organ system failure from HS, other than ventilatory failure secondary to pulmonary edema in patients with poor cardiovascular reserve [43]. Thus, caution is advised in the use of HS in this subset of patients. Anaphylactic reactions and the transmission of blood-borne infections are not a concern with HS solutions. Rapid withdrawal of therapy with HS may result in rebound cerebral edema, leading to elevated ICP or herniation syndromes.

Future directions

While the complex mechanisms of both the osmotic and the nonosmotic action of mannitol have been extensively studied in the cerebral resuscitation paradigm, little is known of the action of HS beyond its osmotic effects. Few studies have demonstrated its nonosmotic effects on CBF and CSF dynamics, but other potential mechanisms of its action require further study. For example, HS has been shown to modulate pro- and anti-inflammatory molecules [52–54], regulate neutrophil-endothelial cell interactions [55], and attenuate polymorphonuclear neutrophil cytotoxicity [56]. While many inflammatory mediators have been implicated in modulating BBB permeability following acute brain injury, the anti-inflammatory in-vivo effects of HS in brain injury remain unexplored.

The molecular mechanisms of cerebral edema are now being considered by several laboratories. In this regard, the glial membrane water channel, aquaporin-4 (AQP4), has received particular attention in the pathogenesis of cerebral edema [57]. Mice deficient in AQP4 have significantly less cerebral edema following water intoxication as well as following focal ischemic insult [58]. Induced hyponatremia causes a pronounced and rapid increase in AQP4 immunoreactivity that is not accompanied by an increase in AQP4 mRNA expression, reflecting secondary confirmational modifications of AQP4 protein [59]. Little is known about the role that AQP4 plays in the pathophysiology of cerebral edema that occurs after brain injury or with brain tumors. Likewise, it is not known whether alteration in AQP4 immunoreactive water channels plays an important role in determining the therapeutic efficacy of HS in these disease entities. Furthermore, the timing, duration, and most efficacious method of instituting therapy (intravenous bolus versus continuous infusion), as well as the specific lesions responsive to HS, remain unclear at the present time, and carefully controlled experiments in appropriate animal models of brain injury are required to address these important questions.

In the clinical paradigm, there are no large randomized clinical trials to date comparing the conventional osmotic agent mannitol versus HS (equiosmolar concentrations) for cerebral resuscitation (effects on elevated ICP and other physiological variables such as CPP) or long-term functional outcomes in critically ill brain-injured patients. Prospective clinical studies will help address this issue.

Conclusions

The management of cerebral edema, with or without elevated ICP, continues to be a challenge for clinicians in the care of patients with acute brain injury. Osmotherapy remains the cornerstone of medical therapy in these critically ill patients. HS solutions have received renewed attention as osmotic agents that can be used therapeutically with minimal side effects. Our experience and those of others suggest that HS is particularly promising in patients with head trauma or postoperative cerebral edema. Studies comparing HS therapy with standard and widely used conventional osmotic agents in cerebral resuscitation are limited. Further studies, in carefully controlled experimental animal models and randomized clinical trials, are required to determine the safety, timing of initiation of therapy, and optimum duration of benefit, as well as the particular cerebral lesions that are most likely to benefit from this therapy. Until these definitive trials are performed, great caution is advised in the clinical use of these solutions.

Acknowledgments. This work is supported in part by US Public Health Service National Institutes of Health grant NS20020. Dr. Bhardwaj is supported in part by the American Heart Association.

References

1. Rosner MJ (1993) Pathophysiology and management of increased intracranial pressure. In: Andrews BT (ed) Neurosurgical Intensive Care, International Edition. McGraw Hill
2. Ropper AH, Rockoff MA (1993) Physiological and Clinical Aspects of Raised Intracranial Pressure. In: Ropper AH (ed) Neurological and Neurosurgical Intensive Care, 3rd edn. Raven, New York
3. Miller RA (1988) Anesthesia for neurosurgery. In: Firestone LL, Lebowitz PW, Cook CE (eds) Clinical Anesthesia Procedures of Massachusetts General Hospital, 3rd edn. Little and Brown, Boston
4. Shapiro HM (1975) Intracranial hypertension: therapeutic and anesthetic considerations. Anesthesiology 43:445–471
5. Bhardwaj A, Ulatowski JA (1999) Cerebral edema: hypertonic saline solutions. Current Treatment Options Neurol 1:179–187
6. Bingaman WE, Frank JI (1995) Malignant cerebral edema and intracranial hypertension. Neurol Clin 13:479–509
7. Hayek DA, Veremakis C (1992) Physiologic concerns during brain resuscitation. In: Civetta JM, Taylor RW, Kirby RR (eds) Critical Care, 2nd edn. Lippincott
8. Minahan RE, Bhardwaj A, Williams MA (1997) Critical care monitoring for cerebrovascular disease. New Horiz 5:406–421
9. Klatzo I (1967) Neuropathological aspects of cerebral edema. J Neuropathol Exp Neurol 26:1–14
10. Rea GL, Rockswold GL (1983) Barbiturate therapy in uncontrolled intracranial hypertension. Neurosurgery 17:510–404
11. Schwab S, Steiner T, Aschoff A, Schwarz S, Steiner HH, Jansen O, Hacke W (1998) Early hemicraniectomy in patients with complete middle cerebral artery infarction. Stroke 29:1888–1893
12. Clifton GL, Miller ER, Choi SC, Levin HS, McCauley S, Smith KR Jr, Muizelaar JP, Wagner FC Jr, Marion DW, Luerssen TG, Chesnut RM, Schwartz M (2001) Lack of effect of induction of hypothermia after acute brain injury. N Engl J Med 344:556–563
13. Paczynski RP (1997) Osmotherapy. Basic concepts and controversies. Crit Care Clin 13:105–129
14. Schell RM, Applegate II RL, Cole DJ (1996) Salt, starch, and water on the brain. J Neurosurg Anesth 8:178–182
15. Zornow MH (1996) Hypertonic saline as a safe and efficacious treatment of intracranial hypertension. J Neurosurg Anesth 8:175–177
16. Gemma M, Cozzi S, Piccoli S, Magrin S, De Vitis A, Cenzato M (1996) Hypertonic saline fluid therapy following brain stem trauma. J Neurosurg Anesthesiol 8:137–141
17. Weed LH, McKibben PS (1919) Experimental alteration of brain bulk. Am J Physiol 48:531–555
18. Fremont-Smith F, Forbes HS (1927) Intravascular and intracranial pressure: an experimental study. Arch Neurol Psychiatr 18:550–564
19. Manninen PH, Lam AM, Gelb AW, Brown SC (1987) The effect of high dose mannitol on serum and urine electrolytes and osmolality in neurosurgical patients. Can J Anesth 34:442–446
20. Rudehill A, Gordon E, Ohman G, Lindqvist C, Andersson P (1993) Pharmacokinetics and effects of mannitol on hemodynamics, blood and cerebrospinal fluid electrolytes, and osmolality during intracranial surgery. J Neurosurg Anesthesiol 5:4–12
21. Marshall LF, Smith RW, Rauscher LA, Shapiro HM (1978) Mannitol dose requirements in brain-injured patients. J Neurosurg 48:169–172
22. Muizelaar JP, Lutz HA, Becker DP (1984) Effect of mannitol on ICP and CBF and correlation with pressure autoregulation in severely head-injured patients. J Neurosurg 61:700–706
23. Mendelow AD, Teasedale GM, Russell T, Flood J, Patterson J, Murray GD (1985) Effect of mannitol on cerebral blood flow and cerebral perfusion pressure in human head injury. J Neurosurg 63:43–48
24. Smith HP, Kelly DL, McWhorter JM, Armstrong D, Johnson R, Transou C, Howard G (1986) Comparison of mannitol regimens in patients with severe head injury undergoing intracranial monitoring. J Neurosurg 65:820–824
25. Cottrell JE, Robustelli A, Post K, Turndorf H (1977) Furosemide- and mannitol-induced changes in intracranial pressure and serum osmolality and electrolytes. Anesthesiology 47:28–30
26. Miller JD, Leech P (1975) Effects of mannitol and steroid therapy on intracranial volume-pressure relationships in patients. J Neurosurg 42:274–281
27. Yu YL, Kumana CR, Lauder IJ, Cheung YK, Chan FL, Kou M, Chan CM, Cheung RT, Fong KY (1992) Treatment of acute cerebral hemorrhage with intravenous glycerol. A double-blind, placebo-controlled, randomized trial. Stroke 23:967–971
28. Todd MM, Tommasino C, Moore S (1985) Cerebral effects of isovolemic hemodilution with a hypertonic saline solution. J Neurosurg 63:944–948
29. Ducey JP, Mozingo DW, Lamiell JM, Okerburg C, Gueller GE (1989) A comparison of the cerebral and cardiovascular effects of complete resuscitation with isotonic and hypertonic saline, hetastarch, and whole blood following hemorrhage. J Trauma 29:1510–1518
30. Schmoker J, Zhuang J, Schackford S (1991) Hypertonic fluid resuscitation improves cerebral oxygen delivery and reduces intracranial pressure after hemorrhagic shock. J Trauma 31:1607–1613
31. Prough DS, Whitley J, Taylor CL, Deal DD, DeWitt DS (1991) Regional cerebral blood flow following resuscitation from hemorrhagic shock with hypertonic saline. Anesthesiology 75: 319–327
32. Mirski MA, Denchev DI, Schnitzer MS, Hanley DF (2000) Comparison between hypertonic saline and mannitol in the reduction of elevated intracranial pressure in a rodent model of acute cerebral injury. J Neurosurg Anesthesiol 12:334–344
33. Bhardwaj A, Harukuni I, Murphy SJ, Alkayed NJ, Koehler RC, Hurn PD, Traystman RJ (2000) Continuous hypertonic saline infusion worsens infarct volume after transient focal ischemia in rats. Stroke 31:1694–1701
34. Himmelseher S, Pfenninger E, Morin P, Kochs E (2001) Hypertonic-hyperoncotic saline differentially affects healthy and glutamate-injured primary rat hippocampal neurons and cerebral astrocytes. J Neurosurg Anesthesiol 13:120–130
35. Toung TJK, Hurn PD, Traystman RJ, Bhardwaj A (2002) Global brain water increases after experimental focal cerebral ischemia: effect of hypertonic saline. Crit Care Med 30:644–649
36. Qureshi AI, Wilson DA, Traystman RJ (1999) Treatment of elevated intracranial pressure in experimental intracerebral hemorrhage: comparison between mannitol and hypertonic saline. Neurosurgery 44:1055–1064
37. Toung TJK, Tyler B, Brem H, Traystman RJ, Kirsch JR, Hurn PD, Bhardwaj A (2001) Hypertonic saline ameliorates cerebral edema associated with experimental brain tumor (abstract). J Neurosurg Anesthesiol 13;4:366
38. James HE, Langfitt TW, Kumar VS, Ghostine SY (1977) Treament of intracranial hypertension. Analysis of 105 consecutive, continuous recordings of intracranial pressure. Acta Neurochir 6:189–200
39. Worthley LI, Cooper DJ, Jones N (1988) Treatment of resistant intracranial hypertension with hypertonic saline: report of two cases. J Neurosurg 68:478–481
40. Weinstabl C, Mayer N, Germann P, Steltzer P, Hammerle AF (1992) Hypertonic, hyperoncotic hydroxy ethyl starch decreases intracranial pressure following neurotrauma (abstract). Anesthesiology 75:201
41. Fisher B, Thomas D, Peterson B (1992) Hypertonic saline lowers raised intracranial pressure in children after head trauma. J Neurosurg Anesthesiol 4:4–10
42. Gemma M, Cozzi S, Tommasino C, Mungo M, Calvi MR, Capriani A, Garancini MP (1997) 7.5% hypertonic saline versus

20% mannitol during elective neurosurgical supratentorial procedures. J Neurosurg Anesth 9:329–334
43. Qureshi AI, Suarez JI, Bhardwaj A, Mirski M, Schnitzer MS, Hanley DF, Ulatowski JA (1998) Use of hypertonic (3%) saline/acetate infusion in the treatment of cerebral edema: effect on intracranial pressure and lateral displacement of the brain. Crit Care Med 26:440–446
44. Shackford SR, Bourguignon PR, Wald SL, Rogers FB, Osler TM, Clark DE (1998) Hypertonic saline resuscitation of patients with head injury: a prospective, randomized clinical trial. J Trauma 44:50–58
45. Suarez JI, Qureshi AI, Bhardwaj A, Williams MA, Schnitzer MS, Mirski M, Hanley DF, Ulatowski JA (1998) Treatment of refractory intracranial hypertension with 23.4% saline. Crit Care Med 26:1118–1122
46. Simma B, Burger R, Falk M, Sacher P, Fanconi S (1998) A prospective, randomized, and controlled study of fluid management in children with severe head injury: lactated Ringer's solution versus hypertonic saline. Crit Care Med 26:1265–1270
47. Qureshi AI, Suarez JI, Castro A, Bhardwaj A (1999) The use of hypertonic saline infusion in treatment of cerebral edema in patients with head trauma. Experience at a single center. J Trauma 47:659–665
48. Suarez JI, Qureshi AI, Parekh PD, Razumovsky A, Tamargo RJ, Bhardwaj A, Ulatowski JA (1999) Adminstration of hypertonic (3%) sodium chloride/acetate in hyponatremic patients with symptomatic vasospasm following subarachnoid hemorrhage. J Neurosurg Anesthesiol 11:178–184
49. Schwarz S, Schwab S, Bertram M, Aschoff A, Hacke W (1998) Effect of hypertonic saline hydroxyethyl starch solution and mannitol in patients with increased intracranial pressure after stroke. Stroke 29:1550–1555
50. Schwarz S, Georgiadis D, Aschoff A, Schwab S (2002) Effects of hypertonic (10%) saline in patients with raised intracranial pressure after stroke. Stroke 33:136–140
51. Soupart A, Penninckx R, Namias B, Stenuit A, Perier O, Decaux G (1996) Brain myelinolysis following hypernatremia in rats. J Neuropathol Exp Neurol 55:106–113
52. Arbabi S, Garcia I, Bauer G, Maier RV (1999) Hypertonic saline induces prostacyclin production via extracellular signal-regulated kinase (ERK) activation. J Surg Res 83:141–146
53. Oreopoulos GD, Hamilton J, Rizoli SB, Fan J, Lu Z, Li YH, Marshall JC, Kapus A, Rotstein OD (2000) In vivo and in vitro modulation of intracellular adhesion molecule (ICAM)-1 expression by hypertonicity. Shock 14:409–414
54. Oreopoulos GD, Bradwell S, Lu Z, Fan J, Khadaroo R, Marshall JC, Li YH, Rotstein OD (2001) Synergistic induction of IL-10 by hypertonic saline solution and lipopolysaccharides in murine peritoneal macrophages. Surgery 130:157–165
55. Angle N, Cabello-Passini R, Hoyt DB, Loomis WH, Shreve A, Namiki S, Junger WG (2000) Hypertonic saline infusion: can it regulate human neutrophil function? Shock 14:503–508
56. Ciesla DJ, Moore EE, Zallen G, Biffl WL, Silliman CC (2000) Hypertonic saline attenuation of polymorphonuclear neutrophil cytotoxicity: timing is everything. J Trauma 48:388–395
57. Wen H, Nagelhus EA, Amiry-Moghaddam M, Arge P, Ottersen OP, Nielsen S (1999) Ontogeny of water transport in rat brain: postnatal expression of the aquaporin-4 water channel. Eur J Neurosci 11:935–945
58. Manley GT, Fujimura M, Ma T, Noshita N, Filiz F, Bollen AW, Chan P, Verkman AS (2000) Aquaporin-4 deletion in mice reduces brain edema after acute water intoxication and ischemic stroke. Nat Med 6:159–163
59. Vajda Z, Promeneur D, Doczi T, Sulyok E, Frokiaer J, Ottersen OP, Nielsen S (2000) Increased aquaporin-4 immunoreactivity in rat brain in response to systemic hyponatremia. Biochem Biophys Res Commun 270:495–503