Fluid Management in Head Injury

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INTRODUCTION

The goals of fluid management for patients with traumatic brain injury (TBI) include replacing intravascular volume deficits, preserving cerebral blood flow (CBF), and minimizing cerebral edema. This chapter will review the basic physiologic principles that influence achievement of those goals.

PHYSIOLOGIC PRINCIPLES

Cell membranes, which are semipermeable to water but less permeable to ions and proteins, partition total body water between the intracellular volume (ICV) and extracellular volume (ECV). Capillary membranes partition ECV into plasma volume (PV) and interstitial fluid volume (ISFV) in proportion to gradients of hydrostatic and oncotic pressure, i.e., the proportion of osmotic pressure attributable to protein. In the brain and spinal cord, capillary membranes are highly permeable to water, but limit the movement of ions such as sodium and of high molecular weight (MW) substances such as colloids. Impermeability of brain capillary membranes to most hydrophobic solutes is a key characteristic of the blood-brain barrier (BBB). In the brain, rapid changes in osmotic gradients, usually resulting from changes in the serum sodium concentration ($[Na^+]$), rapidly redistribute water between the PV and ISFV.

Osmolality and Osmolarity

The term osmolality, which quantifies the number of particles in a solution, is expressed as milliosmoles (mOsm) *per kg of solvent*; *osmolarity* is expressed as mOsm *per L of solution*. The osmolality of 0.9% saline is 308 mOsm/kg, since that solution contains 154 mEq/L (mmol/L) of Na^+; each millimole of sodium is accompanied by a millimole of chloride (Table 1).

Table 1. Osmolarities and oncotic pressures of common intravenous fluids

Fluid	Solute(s) primarily responsible for osmolarity	Osmolarity (mOsm/L)	Osmotic pressure (mm Hg)	Solutes contributing to oncotic pressure	Oncotic pressure (mm Hg)*
Hydroxyethyl starch (6%) (as Hespan™)	Na^+, Cl^-	310	5,983	HES	312
Hydroxyethyl starch (6%) (as Hextend™)	Na^+, Cl^-, lactate	310	5,983	HES	312
Dextran 40 (10%)**	Na^+, Cl^-	~300	5,790	DEX	1693
Albumin (5%)	Na^+, Cl^-	290	5,597	Alb	19
Plasma	Na^+, Cl^-	295	5,694	Prot	21

* = colloid osmotic pressure; D5 = 5% dextrose (glucose); glu = glucose; HES = hydroxyethyl starch; DEX = dextran; Alb = albumin; Prot = serum protein; ** low MW dextran.

When solutions of unequal osmolality are separated by a membrane permeable to water but not solutes, water will move from the solution of lower osmolality into the solution of higher osmolality until both osmolalities equalize. Each difference of one mOsm/kg across a semipermeable membrane generates an osmotic pressure of approximately 19.3 mmHg.

Oncotic Pressure vs. Osmotic Pressure

Oncotic pressure, also termed colloid osmotic pressure, is defined as the osmotic pressure generated by solutes larger than an arbitrary limit (usually 30,000 MW). Albumin, hydroxyethyl starch, dextran 40, and dextran 70 are clinically important compounds that exert oncotic pressure (Table 1). In intravenous fluids, colloids, regardless of their oncotic pressure, contribute so few particles in comparison to the ionic components that their contribution to osmolarity and osmotic pressure is small.

Fluid Movement Between Cerebral Capillaries and Brain Tissue

The gradient between intravascular and interstitial oncotic pressure is partially responsible for preservation of intravascular volume, as expressed in the Starling Equation:

$Q_f = K_f A [(P_c - P_i) - \sigma(\pi_c - \pi_i)]$

where Q_f represents net fluid movement; K_f is the filtration coefficient and A is the surface area of the capillary membrane; P_c is the hydrostatic pressure in the capillary lumen; P_i is interstitial hydrostatic pressure (usually negative); π_c is the colloid osmotic pressure in the capillary plasma; π_i is the colloid osmotic pressure of the fluid in the interstitium; and σ is the reflection coefficient, which ranges from 0 (free diffusion of the solute across the membrane) to 1 (no movement of the solute across the membrane).

In cerebral capillaries, σ for most solutes, including sodium, potassium and chloride as well as plasma proteins, is nearly 1.0, because vascular endothelial cells in the brain and spinal cord form tight junctions [1]. In effect, the BBB functions as an osmometer, i.e., transmembrane movement of water is determined by the relative concentrations of impermeant solutes. In contrast, in systemic capillary beds, electrolytes pass easily from the capillary lumen into the interstitial space. Thus, administration of large volumes of iso-osmolar crystalloid will dilute plasma protein concentrations and result in peripheral edema, but will not generally increase brain water content or intracranial pressure (ICP).

Implications for Care of Patients with Intracranial Pathology

Because osmolality is the primary determinant of water movement across the intact BBB, the administration of excess free water (i.e., in parenteral or enteral fluids in which the $[Na^+]$ is $\leq$ plasma $[Na^+]$), can increase brain water and ICP [2]. Conversely, the iv administration of hyperosmolar mannitol to increase plasma osmolarity will decrease brain water and ICP. Increasing plasma osmolality favors the movement of water into plasma from both the brain interstitial space and the brain intracellular compartment.

If the BBB is intact, theory suggests that colloids should exert minimal effect on cerebral edema. Nevertheless, studies of the influence of colloids vs. crystalloids in animal models of cerebral injury have generated conflicting results. In rats subjected to 10 minutes of severe forebrain ischemia, hemodilution with either 0.9% saline or 6% hydroxyethyl starch (dissolved in 0.9% saline) was not associated with differences in cerebral edema formation, despite approximately a 50% reduction in π_c in the saline group (from 17.2 $\pm$0.8 to 9.0 $\pm$ 0.6 mmHg) [3]. In cryogenically cerebrally injured rats that received 0.9% saline, 6% hetastarch (in 0.9% saline), or 5% albumin (in 0.9% saline), Zornow et al. [4] found no differences in regional water content or ICP. In contrast, in rats subjected to fluid-percussion TBI, Drummond et al. [5] reported that 6% hydroxyethyl starch limited water accumulation in injured brain in contrast to iso-osmolar or hypo-osmolar solutions. One possible explanation is that TBI modifies the permeability of the BBB so that the BBB may behave similarly to the systemic circulation.

Albumin has been used not only for volume replacement in experimental TBI but also as a pharmacologic treatment. In rats after fluid percussion TBI, 25% human serum albumin in a dose of one % of body weight (equivalent to 700 mL – 175 g – in a 70-kg human) given 15 minutes after TBI produced superior neurologic and histologic outcome at seven days after injury in comparison to a similar volume of 0.9% saline [6] . After impact acceleration TBI in rats, intracerebroventricular administration of human serum albumin at one and twelve hours post-TBI significantly reduced brain edema [7]. These findings have yet to be confirmed in clinical trials.

In contrast, hyperosmolar (hypertonic) solutions readily cause fluid flux out of brain tissue in which the BBB remains intact, thereby reducing ICP. In experimental cryogenic brain injury, infusion of a hypertonic solution attenuated the increase in ICP associated with the lesion but did not change the water content of brain tissue at the lesion site or in its immediate vicinity [8]. In effect, "dehydration" of normal brain compensates for edema in injured brain.

CHARACTERISTICS OF INTRAVENOUS FLUIDS

Most solutions used for intravenous administration are categorized as crystalloids or colloids. Crystalloid solutions are subdivided into hypotonic, isotonic, and hypertonic solutions.

Crystalloids are solutions composed solely of low MW (<30,000) solutes, which may be charged (e.g., Na^+, Cl^-) or uncharged (e.g., dextrose or mannitol). By definition, the oncotic (colloid osmotic) pressure of crystalloids is zero. Colloquially, the terms *hypotonic, isotonic, and hypertonic* refer to fluids in which the total osmolarity is less than, equal to, or greater than serum osmolality. Physiologically, the important consideration is whether the fluid has a $[Na^+]$ less than, equal to, or greater than plasma, and thus whether the proportion of water is greater than, equal to, or less than plasma.

Solutions containing free water ($[Na^+]$ substantially less than that of serum), when infused rapidly in large volumes, reduce plasma osmolality, drive water across the BBB into the brain, and increase cerebral water content

and ICP. However, lactated Ringer's solution, often misidentified as "isotonic," actually is mildly hyponatremic and 0.9% saline is mildly hypernatremic (Table 1). Rapid infusion (60 mL/kg over two hours) of lactated Ringer's solution or 0.9% saline in patients undergoing gynecologic surgery was associated, respectively, with a decrease of plasma [Na^+] of nearly 2.0 mEq/L or an increase of plasma [Na^+] of nearly 2.0 mEq/L. These changes are equivalent to decreases and increases in plasma osmotic pressure of approximately 36 mm Hg, with a total difference between the two fluids of approximately 72 mm Hg.

For many years, clinicians have acutely increased plasma osmotic pressure to reduce brain water and ICP. Conventionally, hypertonic mannitol, which cannot pass through the intact BBB, has been the primary agent used for therapeutic brain dehydration. Rapid administration of large doses of mannitol may have a biphasic effect on ICP. Initially, ICP may increase owing to an increased cerebral blood volume as a consequence of the cerebral vasodilatory effects of the acute increase in plasma osmolarity. Subsequently, ICP will decrease owing to the movement of water from the brain interstitial space into the vasculature.

Hypertonic saline solutions, i.e., saline solutions containing [Na^+] in concentrations exceeding 154 mEq/L, are crystalloid solutions that have been used for low-volume resuscitation from hemorrhagic shock, especially in patients with TBI, and as an alternative to mannitol for osmotic reduction of ICP. Weed [9] first suggested nearly 100 years ago that hypertonic saline would reduce brain bulk. In hypovolemic patients who failed to respond to mannitol, iv infusions of small volumes of hypertonic saline solutions rapidly restored blood pressure, improved urinary output, and decreased ICP [10]. Three percent saline decreased ICP in hemodynamically stable, head-injured children [11]. Hypertonic solutions, often combined with colloid, have also been used to reduce ICP in adults undergoing neurosurgical intensive care [12]. Hypertonic solutions should be administered in judicious amounts and with frequent monitoring of plasma osmolality and sodium concentrations. Like other crystalloids, hypertonic saline solutions produce only transient PV expansion.

Hypertonic saline solutions have approximately the same influence on brain water and ICP as mannitol solutions of similar osmolality. When equimolar, rapid intravenous infusions of 200 mL of 20% mannitol or 100 mL of 7.5% saline/6% dextran-70 solution were given over 5 mins to neurological and neurosurgical patients with increased ICP, hypertonic saline dextran exerted a greater effect [13]; however, an equimolar dose of 7.5% saline, because it is almost completely ionized, contains twice the number of osmoles and would be expected to exert a greater effect than mannitol.

Hypertonic saline has been associated, as has 0.9% saline, with hyperchloremic acidosis (Table 2).

Table 2. Production of Hyperchloremic Metabolic Acidosis by Rapid Administration of 0.9% Saline or Hypertonic Saline

Blood gases	**pH**	**7.40**			**7.29**	
	$PaCO_2$	40	mm Hg		29	mm Hg
	[HCO_3^-]	24	mEq/L		14	mEq/L
Electrolytes	**Na^+**	**135**	**mEq/L**		**140**	**mEq/L**
	Cl^-	100	mEq/L		115	mEq/L
	"CO_2"	25	mEq/L		15	mEq/L
	Anion gap	10	mEq/L		10	mEq/L

Hyperchloremic metabolic acidosis, produced as high-chloride solutions displace serum [HCO_3^-] in the ECV, can be distinguished from lactic acidosis and other more ominous causes of metabolic acidosis by demonstrating a normal anion gap. Hyperchloremic acidosis associated with infusion of hypertonic saline usually requires no treatment, but does require differentiation from other causes of metabolic acidosis.

Prehospital clinical trials have evaluated whether rapid infusion of hypertonic solutions might improve outcome when used for resuscitation of hypotensive, head-injured patients. Although early trials suggested a therapeutic effect [14], Cooper et al [15] subsequently reported no difference among 219 TBI patients randomized to prehospital resuscitation beginning with either 250 mL of 7.5% saline or lactated Ringer's solution. Despite differences in serum [Na^+] and [Cl^-], there were no differences in outcome. In humans resuscitated with hypertonic saline, acute increases in serum sodium to 155-160 mEq/L produced no apparent harm [14], specifically no evidence of central pontine myelinolysis, which follows excessively rapid increases of serum [Na^+] during correction of severe, chronic hyponatremia [16].

Colloids

A variety of colloidal solutions are available for clinical use. Hydroxyethyl starch or hetastarch (Hespan™) is a 6% solution of hydrolyzed amylopectin dissolved in 0.9% saline (Table 1). In an uncontrolled series, 14 patients treated with hetastarch for volume expansion to treat cerebral vasospasm developed a significant increase in partial thromboplastin time and six developed clinically significant bleeding; in contrast, 12 patients receiving plasma protein fraction had no increase in partial thromboplastin time and no clinical coagulopathy [17]. Hextend™, a solution of hetastarch that is dissolved in lactated Ringer's solution rather than 0.9% saline, exerts similar effects on intravascular volume and coagulation [18]. Human serum albumin is an effective volume expander that has not been associated with allergic-type reactions and has no intrinsic effects on clotting; however, large doses may contribute to dilutional coagulopathy. Fresh frozen plasma (FFP) should be reserved for use only when there is evidence of a dilutional coagulopathy. FFP can transmit viral diseases [19].

FLUID ADMINISTRATION IN PATIENTS WITH TBI

Patients who sustain TBI often have multiple concurrent injuries and may hemorrhage substantially before arrival in the operating room or intensive care unit. Hypotension is associated with markedly worse outcome in patients with TBI [20], although recent reports suggest that the adverse influence of hypotension in head-injured patients is no greater than the adverse influence of hypotension on outcome in trauma patients without TBI [21]. Physicians caring for hypotensive, head-injured patients should strive to achieve adequate volume resuscitation while considering intracranial hemodynamics and ICP.

Isotonic crystalloid solutions (preferably 0.9% saline) are often the first solutions to be infused in hypotensive trauma patients because they are ready available and inexpensive. Although not considered a standard of care, hypertonic saline solutions may be an option in certain situations, such as hypovolemia accompanied by intracranial hypertension or when sufficient volumes of isotonic crystalloid solutions cannot be rapidly infused. Extensive animal experience supports the efficacy of hypertonic solutions in reversing shock and, usually, decreasing ICP. In those few studies in which hypertonic saline did not reduce ICP [22], it is likely that the BBB was diffusely damaged by trauma or ischemia. In such cases, it is also unlikely that mannitol will be efficacious in reducing ICP.

Colloid solutions are not indicated for fluid management of patients with TBI; however, when massive fluid administration is necessary, colloid solutions have the advantage of producing a more sustained improvement in intravascular volume and may simplify resuscitation. These theoretical advantages have not translated into superior clinical performance. In nearly 7000 critically ill patients randomized to receive either 4% albumin or 0.9% saline for fluid resuscitation, there was no difference in outcome [23]. One noteworthy finding among the subgroup analyses was that mortality was significantly higher (24.5% vs. 15.1%) in trauma patients with brain injury who received albumin [24].

Dextrose-containing solutions are usually not used early in the resuscitation of head-injured patients. Hyperglycemia can induce osmotic diuresis, thereby aggravating hypovolemia, and may aggravate ischemic and traumatic [24] brain injury. In critically ill surgical patients, tight control of plasma glucose (maintenance of plasma glucose between 80 and 110 mg/dL) was associated with reduced mortality and morbidity [25,26]. As a consequence, patients receiving dextrose-containing solutions should be carefully monitored for development of hyperglycemia.

As volume replacement reduces a head-injured patient's hemoglobin concentration towards 8 g/dL, consideration should be given to transfusing red blood cells. Transfusion of packed red blood cells may be indicated at a higher hemoglobin concentration if there is evidence of tissue hypoxia or ongoing uncontrolled hemorrhage. FFP and platelets should be transfused in response to dilutional coagulopathy.

Patients with TBI are at risk for development of hyponatremia during intensive care because of cerebral salt-wasting, which is associated with hypovolemia, or the Syndrome of Inappropriate Antidiuretic Hormone (SIADH), in which blood volume is normal [27]. Acutely, hyponatremia increases brain water content. Compensatory responses to cerebral edema include bulk movement of interstitial fluid into the cerebrospinal fluid and loss of intracellular solutes, including potassium and organic osmolytes [29]. In hypovolemic, hyponatremic patients, blood volume must be restored, usually by infusion of 0.9% saline, and excessive sodium losses must be curtailed. In SIADH, the cornerstones of management are free water restriction and elimination of precipitating causes. Water restriction, sufficient to decrease TBW by 0.5-1.0 L/day, decreases ECV. Even symptomatic hyponatremia should be corrected cautiously. Although delayed correction may result in neurologic injury, inappropriately rapid correction may result in abrupt brain dehydration, central pontine myelinolysis, cerebral hemorrhage, or congestive heart failure. To limit the risk of myelinolysis, plasma [Na^+] may be increased by 1-2 mEq/L/hr; however, plasma [Na^+] should not be increased more than 12 mEq/L in 24 hours or 25 mEq/L in 48 hours [29].

Occasionally, neurogenic (central) diabetes insipidus (DI) may occur in patients after TBI. Diabetes insipidus is characterized by the production of large volumes, as much as one L per hour, of dilute urine in the face of a normal

or elevated plasma osmolality. If untreated, diabetes insipidus can quickly result in severe hypernatremia, hypovolemia, and hypotension. In many patients, before the development of hypernatremia, an increased volume of hypotonic urine suggests an abnormality in water balance [30]. Confirmation of the diagnosis may be obtained by documenting elevated serum osmolality and $[Na^+]$ in conjunction with a low urinary specific gravity or osmolality. Because of the preexisting hyperosmolar/hypernatremic state, infusion of 0.9% saline may actually reduce serum $[Na^+]$. Rapid reduction of serum $[Na^+]$ may cause cerebral edema, seizures or cerebral edema [31]. The water deficit should be replaced over 24-48 hr, and the plasma $[Na^+]$ should not be reduced by more than 1-2 $mEq \bullet L^{-1} \bullet hr^{-1}$. Concomitantly, replacement of endogenous ADH should be initiated with either aqueous vasopressin (5-10 units by intravenous or intramuscular injection) or desmopressin (DDAVP) 1-4 µg subcutaneously or 5-20 µg intranasally every 12-24 hr. DDAVP lacks the vasoconstrictor effects of vasopressin [32].

MONITORING FLUID ADMINISTRATION IN TBI PATIENTS

Two contrasting methods are used to assess the adequacy of intravascular volume. The first, conventional clinical assessment, is appropriate for most patients; the second, goal-directed hemodynamic management, may be superior for high-risk patients. Recently, transesophageal echocardiography (TEE) has shown promise as a means of estimating cardiac dimensions and preload.

Urinary output usually declines precipitously during moderate to severe hypovolemia. Therefore, in the absence of glycosuria or diuretic administration, a urinary output of 0.5-1.0 $ml \bullet kg^{-1} \bullet h^{-1}$ during anesthesia suggests adequate renal perfusion. In TBI patients undergoing extensive procedures, direct arterial pressure measurements are necessary. Direct arterial pressure monitoring may facilitate recognition of hypovolemia, as reflected in increased systolic blood pressure variation accompanying positive pressure ventilation[33,34].

In general, echocardiography is now considered the monitoring technique of choice for evaluation of preload in patients who have received fluid boluses to treat hypotension and who have failed to respond to apparently adequate volumes of fluids[35]. Two methods by which 2-D echo can be used to evaluate ventricular preload are by measurement of ventricular end-diastolic volume (LVEDV; semiquantitative) and by disappearance of the left ventricular cavity at end-systole (qualitative). End-diastolic volumes obtained at the midpapillary transgastric level have been sensitive enough to detect acute changes in preload, even in patients with ventricular wall-motion abnormalities [36,37]. Leung et al. [38] compared the presence of end-systolic cavity obliteration to decreases in LVEDV and reported high sensitivity but poor specificity because of the complex interaction of ventricular contractility and afterload with changes in preload.

SUMMARY

Appropriate fluid therapy for patients with TBI requires an understanding of the basic physical principles that govern the distribution of water between the intracellular and extracellular compartments. In the CNS, unlike peripheral tissues, osmolar gradients are the primary determinants of the movement of water. Therefore, administration of hypertonic solutions (e.g., 20% mannitol) results in a "dehydration" of normal brain tissue with a concomitant decrease in cerebral volume and ICP. Arterial hypotension after brain injury is an ominous sign that correlates with a marked increase in morbidity and mortality. In addition to management of intravascular volume, fluid therapy often must be modified to account for disturbances of $[Na^+]$, which are common in patients with neurologic disease. Various monitoring modalities may help the clinician in the assessment of intravascular volume.

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