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Volume and electrolyte management

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Osmolality is the primary determinant of water movement across the intact blood–brain barrier (BBB), and we can predict that reducing serum osmolality would increase cerebral oedema and intracranial pressure. Brain injury affects the integrity of the BBB to varying degrees. With a complete breakdown of the BBB, there will be no osmotic/oncotic gradient, and water accumulates (brain oedema) consequentially to the pathological process. In regions with very moderate BBB injury, the oncotic gradient may be effective. Finally, osmotherapy is effective in brain areas with normal BBB; hypertonic solutions (mannitol, hypertonic saline) dehydrate normal brain tissue, with a decrease in cerebral volume and intracranial pressure. In patients with brain pathology, volume depletion and/or hypotension greatly increase morbidity and mortality. In addition to management of intravascular volume, fluid therapy must often be modified for water and electrolyte (mainly sodium) disturbances. These are common in patients with neurological disease and need to be adequately treated.

Key words: cerebral perfusion pressure; CBF-targeted therapy; colloid; colloid oncotic pressure; CPP-targeted therapy; crystalloid; haemodilution; hypertonic saline; hypovolaemia; mannitol; osmolality; osmolarity; recombinant activated factor VII.

The goals of fluid management for neurosurgical patients include maintaining intravascular volume, preserving cerebral perfusion pressure, and minimizing cerebral oedema.[1] Cerebral perfusion and haemodynamic stability are essential in the maintenance of neuronal homeostasis; however, the optimal fluid choice for prevention of secondary injury after a neurological insult is unknown.

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Cerebral oedema, a final common pathway of numerous neurological diseases, may rapidly become life-threatening. For a long time, restrictive fluid management has therefore been the treatment of choice in patients with brain pathology growing from fear that fluid administration could enhance cerebral oedema and intracranial hypertension.[2] It is well known that fluid restriction, if pursued to excess (hypovolaemia), may result in episodes of hypotension which can increase intracranial pressure (ICP) and reduce cerebral perfusion pressure (CPP); the consequences can be devastating.[3] On the other hand, crystalloid volume required for optimizing cerebral haemodynamics may increase the risks of systemic organ compromise (e.g. pulmonary oedema, chronic heart failure).

INTRAVASCULAR VOLUME AND HYPOVOLAEMIA

In neurosurgical patients, and very often in the postoperative period, intravascular volume can be depleted, one of the most frequent reasons for this being the use of diuretics.

There is a substantial body of evidence that systemic hypotension independently increases the morbidity and mortality in patients with brain injury.[4,5] Hypotension must be avoided or rapidly corrected, and fluid and volume management should always be undertaken in the light of clinical assessment. Look at skin turgor. Is the tongue dry and furry? Is the patient peripherally shut down, with cold and clammy skin and a prolonged capillary refill time? Is the patient sweating and tachycardic? Usually, a persistently low urine output (<0.5 mL/kg/h) may be indicative of inadequate fluid replacement, which needs prompt treatment. When diuretics and/or mannitol are given, urinary output can be misleading, and thirst, which is as important an early warning sign for volume depletion, is not present if the patient is drowsy or sedated. The patient can be asymptomatic until the circulating volume has decreased by at least 10%. Once the intravascular volume is critically reduced, the perfusion of distal tissues becomes compromised. Hypoperfusion of the brain causes non-specific neurological symptoms, such as confusion and odd behaviour.

Practice points

- confusion is not always a consequence of the neurosurgical procedure
- in taking care of neurosurgical patients, think always of brain *and* intravascular volume
- keep circulating volume as normal as possible, and avoid iatrogenic volume depletion

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Clifton et al retrospectively analysed data from the randomized controlled trial of therapeutic hypothermia.[6] When they analysed individual predictive variables separately, they found that low mean arterial pressure (MAP <70 mmHg) and a fluid balance <594 mL were associated with an increased proportion of patients with poor outcome.[6]

Basic fluid and electrolyte requirements should always be considered in the postoperative period. Table 1 indicates fluid input and output over 24 hours in a healthy 70-kg adult. To calculate volume replacement, the patient's weight and the suspected blood loss (clinical estimation, see Table 2) are needed.

Table 1. Ordinary fluid input and output over 24 hours in a healthy 70-kg adult.

In	
Food	1000 mL
Drink	1200 mL
Metabolic oxidation	300 mL
Out	
Urine	1500 mL
Faeces	100 mL
Insensible (respiration and sweating)	900 mL
Total in and out	2500 mL

In clinical practice, fluid management requires the assessment of circulating blood volume, e.g. to avoid overinfusion. Unfortunately, conventional haemodynamic parameters (blood pressure, heart rate, etc.) can be misleading, and very sophisticated techniques (such as left ventricular end-diastolic area by trans-oesophageal echocardiography, the 'gold standard' for volume status assessment) are not routinely used.[7] It is essential to choose a technique which is simple to perform at the patient's bedside. Our suggestion is to use a 'fluid challenge' test: an intravenous bolus of a fixed volume of crystalloid or colloid is given over a fixed period of time (usually 3–5 min), while the central venous pressure (CVP) is being monitored.

In clinical practice, a formula often used to estimate the quantity of fluid needed for replacement, including the hidden third space, is:

$$\text{Replacement} = \text{Resuscitation} + \text{Maintenance} + \text{Losses}$$

Practice points

- requirements of maintenance fluid are 1.5–2 mL/kg/h (2.5–3.5 L in 24 hours for a 70-kg adult), and these are independent of the type of surgical procedure; daily maintenance of sodium is 1–2 mmol/kg/d, and potassium 1 mmol/kg/d
- as an example, consider a 70-kg patient with an estimated 10% circulatory volume loss. Because 60% of body weight is water, and total water content is around 42 L (70 × 0.6), 10% volume loss equates to 4.2 L (42 × 0.1), which needs replacement, in addition to maintenance requirements
- a fluid challenge is often used both to *assess* and *treat* volume depletion, particularly in acutely ill patients. Monitoring the CVP during this test is often helpful for guiding further fluid administration. For example, if the CVP rises and then falls after a fluid challenge, more fluid is needed

BLOOD LOSS

If blood has been lost and crystalloids are used, the replacement volume is three times that of the estimated blood loss (only a third of that volume remains intravascular). It is less if colloids are chosen (Table 3).

Table 2. Clinical assessment of hypovolaemia in a 70-kg adult patient.				
Blood loss (mL) (% of total volume)	500–750 (10–15)	750–1000 (15–20)	1500–2000 (30–40)	≥2000 (≥40)
Heart rate (beats/min)	<100	>100	>120	≥140
Blood pressure	Normal	Normal	Reduced	Reduced
Pulse pressure	Normal	Reduced	Reduced	Reduced
Capillary return	Normal (<2 sec)	Prolonged	Prolonged	Prolonged
Respiratory rate (breaths/min)	14–20	20–30	30–40	≥35
Urine output (mL/h)	>30	20–30	5–15	Negligible

If a considerable amount of blood is lost, replacement with blood can be appropriate, because anaemia – both at the time of hospital admission and subsequently – is associated with poorer clinical outcome. However, increased organ dysfunction and worse patient outcome are associated with liberal red blood cell (RBC) transfusion strategies, while a 'restrictive transfusion strategy' (Hb 7–9 g/dL) may reduce morbidity and mortality in critically ill patients.[8,9]

Blood transfusion has also been questioned in the neurosurgical population. A recent study in subarachnoid haemorrhage (SAH) patients demonstrated that patients who received RBC transfusion during surgery were at greater risk for poor outcome, and patients who received a transfusion after surgery were at greater risk for vasospasm.[10]

Practice points

- physicians should be cautioned against using the '10/30' haemoglobin and haematocrit trigger for administering RBC transfusions in all patients, and may need to be more tolerant of normovolaemic anaemia
- unless inadequate tissue oxygenation underlies the patient's disease, a more conservative RBC transfusion strategy may be reasonable for many patients after SAH

In trauma patients coagulopathic derangements occur early, and it has been assumed that the use of recombinant activated factor VII (rFVIIa) can correct coagulopathy associated with massive blood loss. rFVIIa was developed specifically for the management of bleeding in haemophiliacs. Several features make rFVIIa an ideal candidate for reversal of coagulopathy in central nervous system (CNS) haemorrhage. It enhances haemostasis at

Table 3. Intravascular volume after infusion of replacement fluid.	
Fluid infused	Intravascular volume increase
1 litre isotonic crystalloid	≈ 250 mL
1 litre 5% albumin	≈ 500 mL
1 litre hetastarch	≈ 750 mL

the site of injury without systemic activation of the coagulation cascade, acting almost immediately. It requires negligible volume for infusion, poses no risk of transfer of blood-borne pathogens, and it obviously is associated with few serious adverse effects.[11] It may improve coagulation in the face of defective platelets or thrombocytopenia, although a platelet count of 50,000 is necessary for rFVIIa to be effective.[12] Despite the severe risks of morbidity and death associated with CNS haemorrhage, the use of rFVIIa in neurosurgery in patients with coagulopathic disorders has lagged behind that in other fields.[13] rFVIIa may become the first therapy to improve outcome in intracerebral haemorrhage.[14] Several case series highlight its use in neurosurgical and trauma patients without premorbid coagulopathy[15,16], and as a therapeutic tool for preventing rehaemorrhage in patients with SAH.[17] Results of an open-label, dose-escalation safety study of rFVIIa in preventing rehaemorrhage were recently published. Ten patients were recruited into the study. There was no evidence of treatment complications in the first nine patients. But the last patient developed middle cerebral artery branch thrombosis contralateral to the aneurysm, which caused the trial to be halted.[17]

Future clinical trials will hopefully answer unresolved questions regarding risk/benefit ratio, indications, optimal dosing, monitoring, and cost-effectiveness of rFVIIa in non-haemophiliac neurosurgical patients.

Practice points

- current evidence does not yet support the use of recombinant factor VII as standard of care in neurosurgery
- rFVIIa may be used in intracerebral haemorrhage and massive perioperative or traumatic bleeding refractory to conventional therapies
- for now, the bedside decision of whether or not to use rFVIIa currently appears to be a matter of surgical judgment, but debates should be resolved by interdisciplinary consensus

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MANAGEMENT OF CEREBRAL PERFUSION PRESSURE

A controversial topic is the goal of CPP, the difference between the MAP and the ICP, especially in head trauma patients.[18] When cerebral autoregulation is impaired and CPP is below the lower limit of autoregulation, cerebral blood flow (CBF) is dependent on CPP. The two accepted strategies are the CPP-targeted management of Rosner et al[19] and the Lund therapy.[20,21]

The approach of Rosner et al is based on the physiological concept termed vasodilatory cascade: a reduction in CPP, secondary to MAP decrease and/or ICP increase, stimulates the cerebral vessels to dilate in order to maintain CBF. The vasodilation further reduces CPP, by increasing cerebral blood volume and ICP. Increasing MAP under this circumstance has been reported to break the cycle and reduce the ICP.[19] In a series of 158 traumatic brain-injured (TBI) adults patients admitted with Glasgow Coma Scale (GCS) scores <7, Rosner et al reported only a 29% mortality, and almost 60% of the patients achieved a good recovery or moderate disability by 6 months post-injury. In this study CPP was maintained at 70–80 mmHg (mean values 85 ± 12 mmHg) using both systemic vasopressors and fluid therapy with hyperosmolar solutions, including mannitol and

hypertonic saline.[19] This approach provided outcomes that were superior to those of an unadjusted control group from the Traumatic Coma Data Bank where ICP management was the primary therapeutic goal.[19] Subsequently, CPP-targeted management was included in the Head Injury Guidelines as a treatment option.[22,23]

The Lund principle includes hypotension, venodilation, and manipulation of the plasma osmolarity. To preserve a normal colloidal oncotic pressure the infusion of albumin and RBCs are allowed, to reduce capillary hydrostatic pressures, MAP is reduced with by reducing MAP metoprolol and clonidine, and to reduce the cerebral blood volume by vasoconstricting precapillary resistance vessels, low-dose thiopental and dihydroergotamine can be applied. Treatments that would favour increasing transcapillary filtration of fluid – including cerebrospinal fluid drainage, high-dose barbiturates, osmotic diuretics, and high CPP – are avoided. Decompressive craniectomy, which can also increase oedema formation, is reserved as a last resort. The Lund approach argues that a high CPP increases oedema formation and aggravates intracranial hypertension. To minimize brain oedema, it emphasizes reduction in capillary hydrostatic pressure.[20,21]

No study has shown any one of these approaches to have outcome superiority.[19,20] A randomized trial has compared the CBF-targeted strategy (CPP kept >70 mmHg) to a conventional ICP-targeted strategy (CPP kept >50 mmHg).[24] The CBF-targeted treatment decreased the time that CPP was <60 mmHg and reduced the incidence of secondary ischaemic events by approximately 50%. This treatment strategy, however, increased fivefold the incidence of acute respiratory distress syndrome, and did not improve long-term neurological outcome.[24,25]

Recently a third approach, advocated by Robertson, recognizes the heterogeneous nature of brain injury and matches the therapy with the immediate pathophysiological issue at hand.[18] Robertson emphasizes that TBI is heterogeneous, and each individual patient has predominant pathophysiological patterns. In addition, the pathophysiology of TBI evolves over time, and treatment that is appropriate in the first few hours after injury may not necessarily be optimal 2 or 3 days after injury.[18]

Table 4 summarizes the main differences between these approaches.

FLUID MANAGEMENT AND THE BRAIN

There are few substantial human data concerning the impact of fluids on the brain that can guide rational fluid management in neurosurgical patients. The optimal fluid choice for prevention of secondary brain damage after neurological insult is unknown. The lack of abundant data makes it difficult to state a confident and clear fluid choice.

Table 4. Management of cerebral perfusion pressure (CPP). CPP management therapies: goal of CPP.

Traditional:	Rosner:	Lund:	Robertson:
ICP-directed therapy	CPP-targeted therapy	brain volume regulation	individualized therapy
CPP not considered	CPP > 70–80 mmHg	CPP > 50–60 mmHg	(a) hypoperfusion/
ICP < 20 mmHg BP	(above lower limit of	(whatever provides	ischaemia: increase CPP
normal	autoregulation)	adequate perfusion)	to improve CBF
			(b) adequate perfusion:
			maintain normal CPP

BP, blood pressure; CBP, cerebral blood flow; ICP, intracranial pressure.
Modified from Robertson (2001, *Anesthesiology* 95: 1513–1517) with permission.

> **Practice points**
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> - the beneficial effect from the CBF-targeted management of reducing secondary ischaemic insults seems to be offset by complications associated with maintaining blood pressure at an increased level
> - based on the available information, there is evidence that elevating the CPP above the threshold for ischaemia via vasopressors and volume expansion may not be beneficial, and may have detrimental cerebral and systemic effects[24,25]
> - a CPP of 60 mmHg provides adequate perfusion for most brain-injured patients[26]; higher CPP levels should probably be reserved for those patients who demonstrate a specific indication for induced hypertension, such as regional or global ischaemia

Practice is most likely institution-specific and is developed from personal experience among physicians.[27] It is possible, however, to examine those factors that influence water movement into the brain and to make some reasonable recommendations.

Physiological principles

Osmotic pressure

This is the hydrostatic force acting to equalize the concentration of *water* on both sides of a membrane impermeable to substances dissolved in that water. Water will move along its concentration gradient until both osmolalities equalize. Each difference of one mOsm/kg across a semipermeable membrane generates an osmotic pressure of approximately 19.3 mmHg. If two solutions of equal concentration are placed across a membrane, there is no driving force.

Osmolarity and osmolality

Osmolarity quantifies the number of particles in a solution, expressed as milliosmoles per liter of solution (mOsm/L). This value is *calculated* by adding up the milliequivalent (mEq) concentrations of the various ions in the solution. *Osmolality* describes the molar number of osmotically active particles per kilogram of solvent (mOsm/kg). This value is *measured* by determining either the freezing point or the vapour pressure of the solution. For most dilute salt solutions, osmolality is equal to or slightly less than osmolarity.

Note that osmotic activity of a solution demands that particles be 'independent'; as NaCl dissociates into Na^+ and Cl^-, two osmotically active particles are created. If electrostatic forces act to prevent dissociation of the two charged particles, osmolality will be reduced.[1]

Colloid oncotic pressure

Oncotic or colloid oncotic pressure (COP) is the osmotic pressure generated by large molecules (e.g. albumin, hydroxyethyl starch, dextran). In biological systems, where vascular membranes are often permeable to small ions but not to large molecules, proteins are the only osmotically active particles. Normal COP is approximately 20 mmHg (or about 1 mOsm/kg).

Fluid movement between capillaries and tissues: Starling equation

The major factors that control fluid movement between the intravascular and extra-vascular spaces are the transcapillary hydrostatic gradient, the osmotic and oncotic gradients, and the relative permeability of the capillary membranes that separate these spaces. The Starling equation[28] describes the forces driving water across vascular membranes:

$$FM = k(P_c + \pi_i - P_i - \pi_c)$$

where FM is fluid movement, k is the filtration coefficient of the capillary wall (i.e. how leaky it is), P_c is the hydrostatic pressure in the capillaries, P_i is the hydrostatic pressure (usually negative) in the interstitial (extravascular) space, and p_i and p_c are interstitial and capillary osmotic pressures, respectively.

Fluid movement is thus proportional to the hydrostatic pressure gradient minus the osmotic pressure gradient across a vessel wall. The magnitude of the osmotic gradient will depend on the relative permeability of the vessels to solutes.

In the *periphery* (muscle, bowel, lung, etc), the capillary endothelium is freely permeable to small molecules and ions but not to large molecules such as proteins. As a result, π is defined only by colloids, and the Starling equation can be simplified by saying that:

• fluid will move into a tissue whenever the hydrostatic gradient increases (either intravascular pressure rises or interstitial pressure falls) or the osmotic gradient decreases.

The intravascular COP is higher than in the interstitium, and draws water back into the vascular space. If COP is reduced – e.g. by infusion of large volumes of iso-osmolar crystalloid – fluid will begin to accumulate in the interstitium. This is familiar to all anaesthesiologists who have seen marked peripheral oedema in patients given many litres of crystalloid during surgery or resuscitation.

By contrast, in the *brain*, where the BBB is normally impermeable to large molecules (plasma proteins and synthetic colloids), and relatively impermeable to many small polar solutes (Na^+, K^+, Cl^-), osmotic pressure is determined by the *total osmotic gradient*. Here, the COP contributes only a tiny fraction (COP $\approx$ 20 mmHg $\approx$ 1 mOsm/kg).

Practice points

• administration of large volumes of iso-osmolar crystalloids will dilute plasma protein concentrations and result in peripheral oedema, but will not generally increase brain water content or ICP

Haemoglobin, haematocrit and haemodilution

One common accompaniment of fluid infusion is a reduction in haemoglobin (Hb) and haematocrit (Hct). The optimal Hb level for patients with cerebrovascular disease is unknown, although haemodilution reduces blood viscosity and is typically accompanied by an increase in CBF.[29,30] In normal brain, the increase in CBF produced

by haemodilution is an active compensatory response to a decrease in arterial oxygen content, identical to that seen with hypoxia. It should be stressed that in the face of brain injury the normal CBF responses to hypoxia and to haemodilution are attenuated, and both changes may contribute to secondary damage. An Hct level of 30–33% gives the optimal combination of viscosity and O_2-carrying capacity and may improve neurological outcome. In contrast, marked haemodilution (Hct < 30%) causes a pronounced reduction in oxygen delivery capacity[30] and can exacerbate brain injury.

Fluids for intravenous administration

Crystalloid is the term commonly applied to solutions that contain water and low-molecular-weight (MW) solutes, which may be charged (e.g. Na^+, Cl^-, Mg^{++}, K^+) or uncharged (e.g. glucose or mannitol). Crystalloids are inexpensive, are easy to store with a long shelf life, are readily available, and come in a variety of formulations (Table 5). They demonstrate a very low incidence of adverse reactions, are effective for use as replacement or maintenance fluids and require no special compatibility testing. Moreover, there are no religious objections to their use.

Crystalloid solutions have a COP of zero and may be hypo-osmolar, iso-osmolar or hyper-osmolar. Crystalloid can be made hyperosmolar by the inclusion of electrolytes (e.g. Na^+ and Cl^-, as in hypertonic saline, HS) or low-molecular-weight solutes such as mannitol (molecular weight 182) or glucose (molecular weight 180).

Table 5. Composition of commonly used intravenous fluids: crystalloids.

Fluids	Osmolarity[a] mOsm/L	Na	Cl	K	Ca	Mg	Lactate	Dextrose
				mEq/L				g/L
5% dextrose in H₂O (D5W)	278							50
5% dextrose in 0.45% NaCl	405	77	77					50
5% dextrose in 0.9% NaCl	561	154	154					50
5% dextrose in Ringer's solution	525	130	109	4	3			50
Ringer's solution	309	147	156	4	4–4.5			
Lactated Ringer's solution	275	130	109	4	3		28	
5% dextrose in lactated Ringer's solution	525	130	109	4	3		28	50
Plasmalyte[b]	298	140	98	5		3		
0.45% NaCl	154	77	77					
0.9% NaCl (normal saline)	308	154	154					
3% NaCl	1026	513	513					
5.0% NaCl	1710	855	855					
7.5% NaCl	2566	1283	1283					
10% NaCl	3424	1712	1712					
23.4% NaCl	8008	4004	4004					
29.2% NaCl	10000	5000	5000					
20% Mannitol	1098	—	—					

[a] osmolarity = calculated value (osmol = mg/molecular weight × 10 × valence).
[b] Acetate 27 mEq/L and gluconate 23 mEq/L.

Hypo-osmolar crystalloids

Large amounts of hypo-osmolar fluids reduce plasma osmolality, drive water across the BBB, and increase cerebral water content and ICP.[2,31] Five per cent dextrose (D5W) is essentially water (the sugar is metabolized very quickly), provides 'free water' which disperses throughout the intracellular and extracellular compartments, and has little use as a resuscitative fluid. As a consequence, hypo-osmolar crystalloids (0.45% NaCl or D5W) should be avoided in neurosurgical patients.

Iso-osmolar crystalloids

Iso-osmolar solutions, with an osmolality ≈ 300 mOsm/L, such as normal saline, Ringer's solution or plasmalyte, do not change plasma osmolality and do not increase brain water content. A note for caution should be addressed concerning commercial lactated Ringer's solution because it is *not truly iso-osmolar with respect to plasma* (Table 3). Its 'measured' osmolality is ≈ 254 mOsmol/kg, which explains why administration of large volumes can reduce plasma osmolality and increase brain water content and ICP.[31,32] Lactated Ringer's solution, as well as Plasmalyte, contain bicarbonate precursors. These anions (e.g. lactate) are the conjugate base to the corresponding acid (e.g. lactic acid). They do not contribute to the development of acidosis, as they are administered with Na^+ rather than H^+ as the cation. The metabolism of lactate in the liver results in production of an equivalent amount of bicarbonate.

Hyper-osmolar crystalloids: mannitol and hypertonic saline

In the presence of a normal BBB, these solutions increase the osmotic gradient between the intravascular and cellular/interstitial compartments (brain to blood). This leads to the reduction of brain water content, brain volume, and ICP.

Mannitol is the primary agent used for therapeutic brain dehydration. It is effective for control of raised ICP at doses of 0.25–1 g/kg, and the smallest possible dose is infused over 10–15 minutes.[33] Mannitol is recommended as the osmotic drug of choice by both the Brain Trauma Foundation and the European Brain Injury Consortium.[26,34]

We still do not know exactly how mannitol works. It may possibly work through two distinct effects on the brain: a rheological action (immediate plasma-expanding effect), which reduces the Hct and blood viscosity, and increases CBF and cerebral oxygen delivery, and an osmotic gradient, establishing between plasma and cells.[35] Mannitol has several limitations: hyperosmolality is a common problem, and a serum osmolarity >320 mOsmol/L is associated with adverse renal and CNS effects.[36] The osmotic diuresis may lead to hypotension, especially in hypovolaemic patients, and, although controversial, accumulation of mannitol in cerebral tissue may lead to a rebound phenomenon and increased ICP.[37,38]

In the case of hypertonic saline (HS), the permeability of the BBB to sodium is low[39], and the reflection coefficient (selectivity of the BBB to a particular substance) of NaCl is more than that of mannitol. This may make HS to a more effective osmotic drug.[40,41] The use of HS for ICP control was discovered from studies on 'small-volume resuscitation'. In patients with TBI and haemorrhagic shock, HS showed the greatest benefit in terms of survival and haemodynamics.[42] The findings that HS may benefit patients with TBI, while preserving or even improving haemodynamic parameters, stimulated further research in patients with SAH[43] or stroke.[44]

The principal disadvantage of HS is the danger of hypernatraemia. During elective supratentorial procedures, we have shown that equal volumes of 20% mannitol and

7.5% HS reduce brain bulk and CSF pressure to the same extent. However, serum sodium increased during the administration of HS and peaked at over 150 mEq/L at the end of the infusion.[45]

HS infusion bears the risk of central pontine myelinolysis in patients with pre-existing chronic hyponatraemia.[46] This has never been reported in conditions of normonatraemia. Magnetic resonance imaging (MRI) or postmortem studies also failed to demonstrate central pontine myelinolysis despite a maximum sodium level of 182 mmol/L.[47,48]

Other adverse effects include the potential for renal failure, rebound increase in ICP, coagulopathies, volume overload, and electrolyte abnormalities.[48] HS also tends to reduce the plasma strong ion difference, and a non-anion gap metabolic acidosis may occur.[49]

Colloids

Colloid is the term used to denote solutions that contain high-MW molecules, either natural (albumin) or synthetic (hetastarches), and have an oncotic pressure similar to that of plasma (Table 6). Some commonly administered colloids include 5% or 25% albumin, plasma, gelatins, hetastarch (hydroxyethyl starch, MW 450), pentastarch (a low-MW hydroxyethyl starch, MW 264), and the dextrans (MW 40 and 70). Dextran and hetastarch are dissolved in normal saline, so that the osmolarity of the solution is approximately 290–310 mOsmol/L.

Colloids remain within the intravascular space for a relatively long time, and are used to sustain blood pressure without complications from fluid overload. The use of colloid is limited because of bleeding complications. In an uncontrolled series, 14 patients treated with hetastarch developed an increase in partial thromboplastin time, and six developed clinically significant bleeding; in contrast, 12 patients receiving plasma protein fraction had no signs of coagulopathy.[50] Small doses of hetastarch (1000 mL/day), however, do not affect coagulation, and it is recommended not to exceed this dosage in TBI patients. For various reasons, some bias also exists for albumin use in this subset of patients. Nevertheless, albumin is an effective volume expander, has not been associated with allergic-type reactions, and has no intrinsic effects on clotting.

Table 6. Composition of commonly used intravenous fluids: colloids.						
Fluid	Na	Cl	K	Ca	Osmolarity[a]	Oncotic pressure
	mEq/L				mOsmol/L	mmHg
Fresh frozen plasma	168	76	3.2	8.2	≈ 300	21
5% Albumin					290	19
Dextran (10%) 40 in 0.9% NaCl	154	154			≈ 310	61
Dextran (6%) 70 in 0.9% NaCl	154	154			≈ 310	19
Hetastarch (6%) in 0.9% NaCl	154	154			≈ 310	31
Hetastarch (10%) in 0.9% NaCl	154	154			≈ 310	82

[a] Osmolarity = calculated value (osmol = mg/molecular weight × 10 × valence).

Hypertonic/hyperoncotic solutions

Recently, attention has been directed at hypertonic/hyperoncotic solutions (typically hypertonic hetastarch or dextran solutions). Because of the haemodynamic stabilizing properties of these fluids in hypovolaemic shock, administration in patients with trauma and TBI might be particularly advantageous for the prevention of secondary ischaemic brain damage.[51] Small volumes of such solutions can restore normovolaemia rapidly, without increasing ICP. They have been successfully used to treat intracranial hypertension in TBI patients[42], in patients with SAH[43], and in patients with stroke.[52]

IMPLICATIONS FOR CARE OF PATIENTS WITH INTRACRANIAL PATHOLOGY

Clinically acceptable fluid restriction has little effect on oedema formation. The first human study on fluid therapy demonstrated that reducing by 50% the 'standard' maintenance volume in neurosurgical patients (2.000 mL/day of 0.45 normal saline in 5% dextrose) increases serum osmolality over about a week.[2] Thus the 'old concept' of benefit from fluid restriction was simply a consequence of an increased osmotic gradient over time.

   The available data indicate that volume replacement and expansion will have no effect on cerebral oedema as long as normal serum osmolality is maintained, and as long as cerebral hydrostatic pressures are not markedly increased (e.g. due to true volume overload and elevated right heart pressures). Whether this is achieved with crystalloid or colloid seems irrelevant, although the *osmolality of the selected fluid is crucial*. It should also be noted that lactated Ringer's solution is not strictly iso-osmotic (measured osmolality 252–255 mOsmol/kg), particularly when administered to patients whose baseline osmolality has been increased by hyperosmolar fluids (mannitol, HS).

In the clinical setting

Calculated versus measured serum osmolality

The reference method to measure *serum* osmolality is the delta-cryoscopic technique. If the technology is not available, and/or it is not always possible to obtain an emergency measurement, osmolality can be calculated from the osmoles that are routinely measured, such as sodium (mmol/L), urea (mg/dL) and glucose (mg/dL):

$$\text{Calculated serum osmolality} = 2 \times (\text{Na}^+) + \text{urea}/2.8 + \text{glucose}/18$$

   Fluid administration that results in a reduction in osmolality should be avoided. Small volumes of lactated Ringer's (1–3 L) are unlikely to be detrimental and can be safely used. If large volumes are needed (blood loss or other source of volume loss), a change to a more isotonic fluid is probably advisable, such as normal saline (NS), taking into consideration that large and rapid infusion of NS can induce a dose-dependent hyperchloraemic metabolic acidosis.[53] Whether this acid–base abnormality is, in fact, harmful remains unclear.[54] Usually, hyperchloraemic metabolic acidosis requires no treatment, but does require differentiation from other causes of metabolic acidosis (hyperchloraemic metabolic acidosis has a normal anion gap).

If large volumes are needed, a combination of isotonic crystalloids and colloids (Tables 3 and 4) may be the best choice. Hetastarch should be used with caution because of possible induction of coagulatory disturbances.[50] Dextran-40 interferes with normal platelet function and is therefore not advisable for patients with intracranial pathology, other than to improve rheology (such as in ischaemic brain diseases).

Practice points

- our recommendation is that serum osmolality be checked repeatedly, with the goal being either to maintain osmolality within physiological ranges or to increase it slightly
- be advised that calculation of osmolality introduces a bias, overestimating osmolality in the lower ranges and underestimating it in the higher ranges
- these recommendations should not be interpreted as 'give all the isotonic fluid you like'; volume *overload* can have detrimental effects on ICP, by increasing cerebral blood volume or by hydrostatically driven oedema formation

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Glucose

Salt-free solutions containing glucose ('free water') are avoided in patients with brain pathology. Furthermore, there is solid evidence that *excessive glucose exacerbates neurological damage* and can worsen outcome from both focal and global ischaemia.[55] Glucose metabolism enhances tissue acidosis in ischaemic areas, although exactly why hyperglycaemia worsens outcome has not yet been completely elucidated.[56] Several clinical studies have indicated a negative relationship between plasma glucose on admission and outcome in patients after stroke, cardiac arrest, and head injury, and that hyperglycaemia is an independent predictor of poorer outcomes, particularly mortality.[57] Thus, it is prudent to withhold glucose-containing fluids from acute TBI and elective surgical patients. This caveat does not apply to parenteral nutrition therapies, possibly because such solutions are typically started several days after the primary insult, and insulin is usually administered. While aggressive control of hyperglycaemia by insulin therapy improves morbidity and mortality in critical ill surgical patients, conclusive data in patients with brain damage are still lacking.[58,59]

Practice points

- in neurosurgical patients blood sugar should be controlled carefully, the goal being to avoid both hypo- and hyperglycaemia and to maintain glucose between 100 and 150 mg/dL. Glucose-containing solutions should be withheld, except in the case of neonates and patients with diabetes, in whom hypoglycaemia can occur very rapidly and can be detrimental

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Haemodilution

The one situation in which haemodilution might be beneficial is the period during and immediately after a focal cerebral ischaemic event. Several animal studies have shown

that regional oxygen delivery may be increased (or at least better maintained) in the face of modest haemodilution (Hct approximately 30%), with improvement in CBF and reduction in infarction volume. In spite of this, several clinical trials have failed to demonstrate any benefit from haemodilution in stroke patients, except in those who were polycythaemic upon hospital admission. Moreover, haemodilution has not been shown to improve survival or functional outcome.[60]

What clinical lesson can be learned from the work on haemodilution? It is our opinion that in elective neurosurgical patients and patients suffering from head injuries, haemodilution to an Hct below 30–35% is unlikely to be 'beneficial'. Haemodilution to 30–35% might be better tolerated in patients at risk for focal ischaemia. Nevertheless, active attempts to lower Hct are probably not advisable at the present time.

Subarachnoid haemorrhage

When treating patients with SAH two problems should be considered: hyponatraemia and hypovolaemia. Patients with SAH develop hypovolaemia, haemodynamic depression, and increased RBC aggregability.[61] The cause of relative hypovolaemia is multifactorial, and hyponatraemia results from an increased release of a brain natriuretic factor.[62] The triple-H therapy – a combination of induced hypertension, hypervolaemia, and haemodilution – is a strategy widely accepted to prevent/treat cerebral vasospasm after aneurismal SAH. Hypervolaemic haemodilution therapy decreases the Hct level and RBC aggregability while increasing cardiac output.[63] This type of hyperdynamic management and manipulation of blood viscosity counteracts the reduction in cerebral and circulating blood volume that generally occurs with cerebral vasospasm.[61,62] Triple-H therapy theoretically improves CBF to regions of hypoperfusion; however, although this paradigm has gained widespread acceptance over the last 20 years, it has never been extensively studied. It is not clear whether the critical factor is hypertension or hypervolaemia or both.[64] Volume loading is usually performed with colloids, and great care is required to avoid reduction in serum osmolality. Otherwise, this will increase water content in ischaemic as well as normal brain.

Water and electrolyte disturbances

Table 7 summarizes the principal differences between the most common water and electrolyte disturbances in patients with brain pathology.

Diabetes insipidus

Diabetes insipidus (DI) often occurs with pituitary and hypothalamic lesions, but it can also develop in case of other cerebral pathology, such as head trauma, bacterial meningitis, intracranial surgery, phenytoin use, and alcohol intoxication. Patients with markedly elevated ICP and brain death also commonly present with DI. Diabetes insipidus is characterized by the production of large volumes of dilute urine in the face of a normal or elevated plasma osmolality, caused by the decreased secretion of antidiuretic hormone (ADH). This results in failure of tubular reabsorption of water. Polyuria (more than 30 mL/kg/h or, in an adult, more than 200 mL/hour), progressive dehydration, and hypernatraemia occur subsequently. DI is present when urinary output is excessive. The urine osmolality is inappropriately low relative to serum osmolality (which is above normal because of water loss), and the urinary specific gravity is <1.002. The management of DI requires restoration of normal serum sodium, along

Table 7. Principal water and electrolyte disorders.		DI	SIADH	CSWS
Aetiology		Reduced secretion of ADH	Excessive release of ADH	Release of brain natriuretic factor
Urine	Output	>30 mL/kg/h		
	Specific gravity	<1.002		
	Sodium	<15 mEq/L	>20 mEq/L	>50 mEq/L
	Osmolality versus serum osmolality	Lower	Higher	Higher
Serum	Sodium	Hypernatraemia	Hyponatraemia	Hyponatraemia
	Osmolality	Hyperosmolality	Hypo-osmolality	
Intravascular volume		Reduced	Normal or increased	Reduced

ADH, antidiuretic hormone; CSWS, cerebral salt-wasting syndrome; DI, diabetes insipidus; SIADH, syndrome of inappropriate ADH secretion.

with careful balancing of intake and output to avoid fluid overload. The water deficit should be replaced over 24–48 h, and hypernatraemia should not be reduced by more than 1–2 mEq/L/h, because rapid reduction may cause seizures or cerebral oedema. The patient should receive hourly maintenance fluids (Table 8). Half-normal saline and free water are commonly used as replacement fluids, with appropriate potassium supplementation. Serum sodium, potassium, and glucose are to be checked frequently.

If the urinary output is >300 mL/h for 2 hours, it is now standard practice to administer aqueous vasopressin (5–10 IU, intramuscularly or subcutaneously every 6 hours) or the synthetic analogue of ADH, desmopressin acetate (0.5–2 μg intravenously every 8 hours, or 10–20 μg by nasal inhalation).

Syndrome of inappropriate ADH secretion

Various cerebral pathological processes (especially head trauma) can cause excessive release of ADH, which leads to the continued renal excretion of sodium (more than 20 mEq/L), despite hyponatraemia and associated hypo-osmolality.[65] Urinary osmolality is therefore high relative to serum osmolality. Syndrome of inappropriate ADH secretion (SIADH) can also result from over-administration of free water in patients who cannot excrete free water because of excess ADH.

The mainstay of treatment of SIADH is fluid restriction to 1.000 mL/24 hours of iso-osmolar solution. If hyponatraemia is severe (<110–115 mEq/L), administration of hypertonic saline (3–5%) and furosemide might be appropriate. Since rapid correction of hyponatraemia has been associated with the occurrence of central pontine myelinolysis, it is advisable to restore serum sodium at a rate of about 2 mEq/L/h.

Table 8. Management of diabetes insipidus.
Hourly monitoring of urinary output
Maintenance fluids = 75% of the previous hour's urinary output *or*
Maintenance fluids = the previous hour's urinary output −50 mL
If urinary output >300 mL/h give vasopressin or desmopressin

Cerebral salt wasting syndrome

Cerebral salt wasting syndrome (CSWS) is characterized by hyponatraemia, volume contraction, and high urine sodium concentration (>50 mEq/L). This syndrome is frequently seen in patients after SAH, and the causative factor seems to be an increased release of a natriuretic factor from the brain.[62] The therapy is to re-establish normovolaemia with the administration of sodium-containing solutions.

Practice points

- the distinction between SIADH and CSWS is very important because treatment of these two syndromes is quite different: fluid restriction versus fluid infusion
- it should be stressed that in patients with SAH, in whom normo- to hypervolaemia is advocated, fluid restriction (i.e. further volume contraction) might be especially deleterious

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CONCLUSION

Haemodynamic stability and maintenance of cerebral perfusion pressure are crucial to the treatment of patients with intracranial pathology. Fluid management, essential in achieving these goals, requires a clear understanding of the cerebral pathophysiology, always keeping in mind the effects of the fluids on the rest of the body, since we treat the patient and not only the brain.

In the last three decades fluid management of the neurosurgical patient has advanced rapidly, going from 'run them dry' to 'run them isovolaemic, isotonic, and iso-oncotic'. However, important questions still remain regarding the induction of potential complications caused by current fluid management strategies. A comparison of the advantages of different fluid formulations in a variety of clinical and neurosurgical circumstances is lacking.

Research agenda

- water is 'turned on' and 'turned off' by membrane proteins that function as water conduits and are called *aquaporins*; 13 variants of aquaporin have been found in animals and humans.[66] Understanding how aquaporins work and how they are affected by brain pathology will be a future research field in fluid management of the neurosurgical patient
- very few clinical evidence-based data exist on fluid management in the patient with brain pathology. We need well-designed randomized clinical trials on the cerebral effects of different fluids and/or association of volume and fluid therapy in a variety of clinical circumstances
- the more recently introduced brain-imaging techniques may help to understand the movement of water and electrolytes within the human brain

Practice points

- movement of water between the normal brain and the intravascular space is dependent on osmotic gradients
- reducing serum osmolality by administration of free water or hypotonic crystalloid solutions (0.45% NaCl) results in oedema formation in all tissues, including normal brain tissue
- reduction of colloid oncotic pressure with maintenance of serum osmolality is associated with increased water content in many tissues, but not in the normal brain; colloid solutions exert little influence on brain water content and ICP
- in the setting of brain injury, reducing serum osmolality increases oedema and ICP. Therefore, the objective of fluid management in neurosurgery is to avoid reduction of serum osmolality. Reduction of COP, with careful maintenance of osmolality, does not increase oedema in the injured brain
- hypertonic solutions: mannitol decreases brain water content in normal brain and is commonly used to reduce ICP; hypertonic saline decreases brain water content and ICP, but can cause hypernatraemia
- glucose-containing solutions should not be used in patients with brain pathology and are avoided in patients at risk for brain ischaemia
- fluid restriction minimally affects cerebral oedema and, if overzealously pursued, can lead to haemodynamic instability, which is detrimental in neurosurgical patients
- isotonic crystalloid solutions are widely used to maintain and/or restore intravascular volume
- the consequences of large fluid doses, independent of agent, remain under investigation; adult respiratory distress syndrome developed five times more frequently in patients who had undergone a hypertensive CBF-targeted protocol than in patients treated with a less stringent ICP-targeted protocol

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