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The use of crystalloids in traumatic brain injury

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Abstract

Fluid therapy is one of the most important treatments in patients with traumatic brain injury (TBI) as both hypo- and hypervolaemia can cause harm. The main goals of fluid therapy for patients with TBI are to optimize cerebral perfusion and to maintain adequate cerebral oxygenation. The avoidance of cerebral oedema is clearly essential. The current weight of evidence in the published literature suggests that albumin therapy is harmful and plasma substitutes have failed to demonstrate superiority over crystalloids solutions. Crystalloids are the most common fluids administered in patients with TBI. However, differences in their composition may affect coagulation and plasma tonicity and acid-base homeostasis. The choice of the ideal crystalloid fluid in TBI should be made based on tonicity, type of buffer used and volume status. Hypotonic fluids buffered with substances altering blood coagulation should be avoided in clinical practice. The prescriber remains faced with choices about the tonicity and pH buffering capability of fluid therapy, which we review here.

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Solutions of inorganic ions and small organic molecules dissolved in water are referred to as crystalloids. They are far more widely used than colloids which contain a larger molecular weight solute expected to contribute to the colloid osmotic pressure gradient across capillaries. Infused crystalloids influence electrolyte, acid-balance and osmotic homeostasis in all the recognized body fluid compartments. The ideal crystalloid solution is often defined as a fluid which is similar to interstitial fluid and so would not affect electrolyte or the acid-base balance after intravenous administration [1–3]. Bicarbonate dialysate solutions are available with or without potassium, and accommodating the prescriber's preference for calcium and magnesium concentrations (e.g. www.bbraunusa.com/products.html?prid=PRID00007061). Although their only disadvantage is that they are usually supplied in 5 litre bags, the resourceful clinician should be able to create a local policy for their safe use on the ICU. It has been suggested that clinicians should pay more attention to the type of fluid used, particularly in critically ill patients treated for traumatic brain injury (TBI), sepsis, septic shock or acute kidney injury (AKI) [4–6].

REGULATION OF FLUIDS IN THE BRAIN

The central volume of distribution of infused crystalloids is essentially the whole of the intravascular fluid including the glycocalyx layers. Equilibrium with the tissue volume of distribution depends on the transendothelial filtration rate (Jv) and the return of interstitial fluid to the blood via lymph nodes or the thoracic duct (Qlymph). Jv is itself determined by the transendothelial pressure gradient and the transendothelial resistance to flow (reciprocal of hydraulic conduct-

Table 1. Ions in cerebrospinal fluid (CSF), brain interstitial fluid (BISF), plasma and interstitial fluid [7, 12]

	CSF/BISF	Plasma	Interstitial fluid
pH	7.3	7.35 – 7.45	7.38–7.42
Na^+ (mM)	152–156	135–145	139–146
K^+ (mM)	2.86–3	3.6–4.5	2.9–4
Cl^- (mM)	120	110–117	110–113
$HCO3^-$ (mM)	22–24	20–24	26–28
Ca^{2+} (mM)	1.14	2.1–2.5	2
Mg^{2+} (mM)	1.1	0.8–1.2	1.2–1.4

ance Lp) [7]. By definition, while isotonic solutions have no effect on intracellular water content, hypotonic solutions pose a threat to intracranial pressure because an acute fall in the tonicity of plasma causes brain cells to swell. Extracellular oedema occurs when the net variance between Jv and QLymph results in pathological interstitial fluid excess. It used to be believed that the brain was unusual in having no lymphatic system, but such a system was discovered in 2015 [8]. It also used to be believed that biophysical osmotic therapy with colloids would reduce interstitial oedema, but this is now known to be untrue [7]. Although neuronal cells can compensate for an increase in brain water content, especially by regulating brain interstitial fluid (BISF), via active depletion of intracellular osmotic solutions, these mechanisms may also trigger an apoptotic pathway [9, 10]. Patients treated for TBI are especially susceptible to disturbances in blood tonicity and electrolyte disorders. Physiologically, the inorganic ions in brain fluids depend on permeability of two interfaces: the choroid plexus and the brain blood-barrier (BBB). The choroid plexus produces cerebrospinal fluid (CSF), while the BBB generates BISF that drains into the CSF. The composition of BISF depends primarily on the transport of the BBB and plasma osmolality while its volume depends on intra-cranial pressure (ICP) and cerebral perfusion pressure (CBP) [10, 11]. It should be noted that while concentrations of K^+, Na^+, Ca^{2+} and Cl^- are very close in BISF and CSF, they are significantly different from those in blood plasma (Table 1). Small molecules move freely between BISF and CSF whereas large molecules move slowly across the boundaries between BISF and CSF [11, 12]. Some authors have shown that 70 – 90% of isotopically marked water in the blood perfusing the brain go over the BBB in a single pass [10, 13–16]. It can be estimated that the total net water flow into the brain amounts to '680 L per day when cerebral blood flow (CBF) is 700–800 mL per min. In the smallest brain capillaries, the brain water movements depend mainly on the hydrostatic and total osmotic gradients between both sides of the BBB [15, 16]. However, the permeability of brain microvessels to Na^+ and Cl^- is 1000-fold lower than in peripheral vessels, which plays a crucial role for the water shift to the brain [10, 17]. It has been estimated that 1 mM concentration difference for NaCl across the BBB changes hydrostatic pressure difference by 38 mm Hg [15, 16, 18, 19]. Based on this assumption, the rate of fluid shifts across BBB is strictly dependent on solute transport and the volume of BISF is determined by the solute concentration in BISF and the plasma osmolality [10]. Even small changes in blood osmolality of 1 mOsm L^{-1} increase the pressure of fluid shifts across the BBB at 19 mm Hg, and a decrease in plasma osmolality by approximately 3%, i.e. from 288 to 280 mOsm kg^{-1} H_2O, increases brain volume by 3% and decreases intra-cranial blood and/or CSF volume by as much as 30% [10, 20]. Therefore, hypotonic solutions have not been recommended for patients with traumatic brain injury as they increase brain volume (Grade 1C) [21]. The daily production of CSF is around 600–700 mL (CSF is produced at a rate of 0.2–0.7 mL min^{-1}) and the turnover of entire volume of CSF is three to four times per day.

ALTERATIONS IN BLOOD BRAIN BARRIER

In general, TBI coexists with an increase in BBB permeability, which is an early consequence of injury. The greatest destruction in the BBB is detected in the pericontusional area during the first 48 hours after TBI [22]. A transcapillary leakage leads to a decline in osmotic buffering capacity of small solutes and rapid water filtration along hydrostatic and osmotic gradients. An increase in BBB permeability also favours a raised shift of osmotically important molecules such as sodium, disturbing BISF tonicity [15]. Therefore, some authors have suggested that uncontrolled extravasation of crystalloids through an injured BBB should be compensated by an increase in plasma oncotic pressure as an opposing force to fluid filtration [23, 24]. Bulk flow of water through a disrupted BBB is driven by osmotic and hydrostatic forces, produced by alterations in ion transport. If the concentrations of solutes in BISF and nervous cells is constant, small changes in plasma ions content moderately affect water and solutes shift into BISF. However, every TBI increases BBB permeability resulting in brain oedema following pathological osmotic-driven fluid flow into the brain.

A peri-injury hypotension treated with overzealous crystalloid infusion significantly increases brain water content leading to cytotoxic oedema [25].

THE ROLE FOR HYPERTONIC SOLUTIONS

A relatively small volume (4 mL kg^{-1}) of hypertonic saline 3–7% can significantly reduce ICP, correct CBF and improve cerebral oxygen delivery [26]. Elliot *et al.* [27] showed in an experimental study that the use of hypertonic saline treatment resulted in a significant decrease in the number of hypertrophic astrocytes, together with a reduction of stress-related inflammatory response, and that this was associated with improved outcomes. Hypertonic saline also suppresses production of proinflammatory cytokines in activated microglia and increases the expression of inducible nitric oxide synthase in the peri-ischaemic area [28]. It is remarkable that the extreme chloride load of hypertonic saline seems quite safe in reality. Although hypertonic saline is also used in the emergency medicine setting, the fourth edition of the guidelines for the management of severe TBI has not supported hyperosmolar therapy and only recommends mannitol as an effective treatment in patients with elevated ICP [29–31].

THE ROLE OF BALANCED CRYSTALLOID SOLUTIONS

Balanced solutions and normal saline are both advocated by experts to treat hypovolaemia in TBI patients. There is no reason why both may not be used if plasma chloride concentrations are being monitored. The case for balanced salt solutions includes the occurrence of dilution hyperchloremic acidosis following massive saline infusion [32, 33]. Indeed, infusion of large volumes of normal saline commonly leads to dilution hyperchloremic acidosis, particularly in hypovolaemic patients with impaired kidney function or perfusion [33]. Evidence has been produced that massive infusion of chloride-rich fluids leads to renal ischemia following interstitial oedema, and reduces glomerular filtration following arterial vasoconstriction, hence increasing the risk of AKI [34, 35]. Infusion of 20 mL kg^{-1} of chloride solution (9 L of 0.9% NaCl) decreases base excess by 10 mmol L^{-1} in a typical 70 kg patient, suggesting an inverse linear relationship between base excess and the amount of chloride administration [4]. It should be noted that the occurrence of AKI has been reported in 9–23% of patients with TBI, and depends on age, severity of TBI and daily fluid balance [36]. Some authors have also documented a deleterious effect of normal saline when irrigated directly on an injured brain. A decrease of pH and rapid electrolyte disorders in BISF lead to neural damage and increase the risk of hematoma recurrence [37, 38]. The use of balanced solutions may prevent all the above-mentioned effects and may be safer than normal saline when given as intravenous infusion or direct irrigation on the brain [37, 39].

Isotonic balanced salt solutions reduce the occurrence of dilution hyperchloremic acidosis and do not affect ICP and the number of episodes of intra-cranial hypertension (ICH) [39]. Unfortunately, some solutions are hypo-osmotic and their in-vivo (real) osmolality (tonicity) is lower than the theoretical or plasma tonicity (Table 2) [6, 40]. Such differences result from different plasma and fluid compositions. Generally, all therapeutic fluids contain cations and anions (Na^+, K^+, Mg^{2+}, Ca^{2+}, Cl^-) buffered by anions including malate, lactate, citrate or acetate, whereas plasma cations are buffered by sulphate, phosphate, organic acids and some proteins. Different content of fluid ions has a significant impact on strong ion difference (SID) affecting the plasma acid-base state and plasma electrolyte concentrations. Despite their different composition, some authors have documented similar unfavourable effects of Plasma-Lyte® 148 and 0.9% NaCl on kidney function in 12 healthy volunteers [41]. Although both fluids expanded the intravascular volume to the same degree, extravascular fluid disorders were significantly greater in the 0.9% NaCl compared to the Plasma-Lyte® group. Another clinical study has documented a similar occurrence of AKI in critically ill patients treated with Plasma-Lyte and 0.9% NaCl [42]. An experimental study comparing 0.9% NaCl versus Plasma-Lyte® and Ringer's lactate in haemorrhagic shock has presented a significantly better 24-hour-survival rate in animals receiving Ringer's lactate compared to Plasma-Lyte® or saline (67% vs 30%) [43]. While the composition and tonicity of crystalloid solutions may have an impact on survival after fluid resuscitation from hypovolaemia, the case for normal saline is that it is safe, cheap and widely available [44]. Until randomized clinical trial evidence is available, clinical judgment may be used to choose between normal saline or a balanced salt solution of adequate tonicity for resuscitation from hypovolaemia.

EFFECTS OF CRYSTALLOID SOLUTIONS ON COAGULATION

Crystalloid-induced alterations in coagulation should be a factor determining the choice of fluid in patients treated for TBI. General disorders in coagulation following volume-related blood dilution, as well as some disorders related to specific crystalloid composition (such as presence of citrate) may increase the risk for intracranial (re)bleeding resulting in a worse clinical outcome. It should be noted that acute idiopathic coagulopathy disorders occur in 59% of all patients with TBI (7–86.1%), and are frequently observed in patients with parenchymal injury [45–48]. Posttraumatic coagulopathy has been noted more frequently in patients with isolated TBI than injuries without TBI, and this has not been dependent on the severity of TBI [48]. Acute coagulation disorders are associated with higher mortality, particularly when they develop within the first 24 hours after TBI [46, 47]. Citrate,

Table 2. Composition of the most popular fluid in Poland

	0,9% NaCl	Ringer's Solution	Multielectrolyte fluid (PWE)	Optilyte	Plasmalyte	Sterofundin ISO	Sterofundin
Na^+ (mmol L^{-1})	154	130	141	141	140	145	140
Cl^- (mmol L^{-1})	154	109	109	109	98	127	106
Ca^{2+} (mmol L^{-1})	–	3	2	2		2,5	2,5
Mg^{2+} (mmol L^{-1})	–	–	1	1	1,5	1	1
K^+ (mmol L^{-1})	–	4	5	5	5	4	4
Buffered anions: acetate	–	–	34	34	27	24	
Buffered anions: citrate	–	–	3	3	–	–	
Buffered anions: gluconate	–	–	–	–	23	–	–
Buffered anions: lactate	–	28	–		–	–	45
Buffered anions: malate	–	–	–	–	–	5	–
SID	0	28	43	43	50	29	45
pH	4.5–7	5–7	5.5–7.5	5.5–7.5	4–8	5.1–5.9	4.5–7.5
Osmolarity „in vitro" (mOsm L^{-1})	308	273	295	295	295	309	299
Osmolality „in vivo" mOsm kg^{-1} H_2O)	285	256	273	273	273	286	277
Tonicity	Isotonic	Hypotonic	Hypotonic	Hypotonic	Hypotonic	Isotonic	Hypotonic

SID: strong ions difference

contained in some fluids, binds blood to ionized calcium and intensifies or induces coagulation disorders. Similar effects may be induced by massive infusion of packed red blood cells and platelets, as these products contain high citrate concentrations [21, 49]. Therefore, the control of ionized calcium has been strongly recommended in the European guideline on management of major bleeding and coagulopathy following trauma (recommendation 30) [21]. The current goal-directed protocols advocating the use of massive fluid resuscitation have suggested using fresh frozen plasma with packed red blood cells to maintain Hb of 7–9 g dL^{-1} (recommendation 17) underlining, that a low initial Hb level indicates severe bleeding coagulopathy (recommendation 10). In that case the use of crystalloids should be limited [21]. Initial military experience showed that use of plasma and packed red blood cells at the ratio 1:1 improved haemostasis, the time of artificial ventilation and final outcome [50]. However, the risk of acute respiratory distress syndrome (ARDS) increases with increasing number of fresh frozen plasma units and/or crystalloids, whereas crystalloids infused with packed red blood cells do not increase the risk for ARDS [51, 52]. An increased risk for ARDS is associated with the male sex and depends on the volume and duration of crystalloid infusion [52]. A quick infusion of crystalloids or plasma not only increases the risk for ARDS, but also for brain oedema. An experimental study has documented that rapid infusion of crystalloids and plasma following TBI and shock has been associated with brain swelling and an increase in ICP despite quick correction of peripheral oxygenation and cardiac output [53]. Moreover, fast infusion of crystalloid solutions has increased lesion size. Slow, continuous infusion of these fluids has been shown to be safe and is devoid of adverse effects.

THE ROLE OF BUFFERS IN BALANCED SOLUTIONS

Different crystalloids are buffered by different substances that can be used as a fuel for the brain or substrates in the Cori cycle. Exogenous lactate is a well-established fuel for the brain in situations of increased energy demand. In experimental studies of TBI, lactate infusion preserved extracellular glucose levels, improved mitochondrial oxidative respiration and outcomes [54, 55]. A previous clinical study has documented a significant correction of brain dysfunction following severe hypoglycaemia [56].

Little is known about the effects of citrate, acetate, malate and gluconate on brain metabolism. Gluconate is mainly excreted with urine. Yet, only one study has documented an immediate elevation of unmeasured anions in cardiac surgery patients receiving a gluconate-based buffered crystalloid (Plasma-Lyte® 148) [57]. Another study showed that the use of Plasma-Lyte 148 as a priming fluid for cardiopulmonary bypass resulted in supra-physiological concentrations of acetate and gluconate and an increase in plasma IL-6 concentrations [58].

Citrate is metabolised in the liver, and its metabolism may be significantly impaired in shock, hypothermia and in patients with hepatic insufficiency [59]. Citrate serum concentrations have been suggested as potential biomarkers

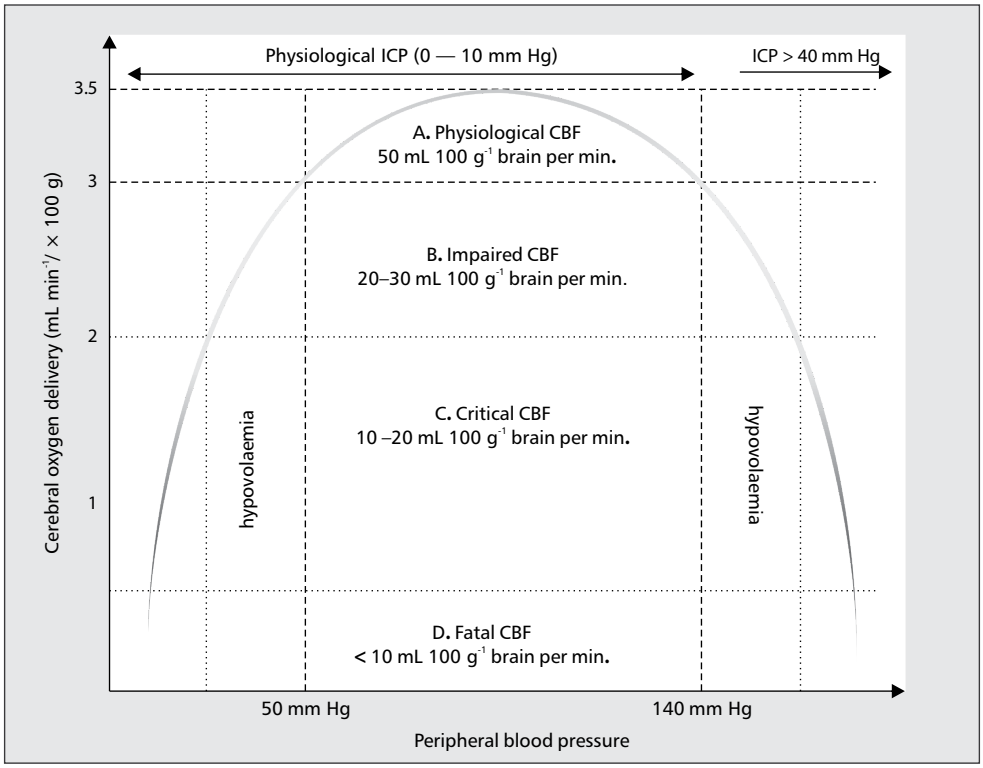

Figure 1. Changes in Cerebral Perfusion Pressure (CPP) in accordance to peripheral blood pressure. **A**. Physiologically, intra-cranial pressure (ICP) ranges between 0–10 mm Hg. **B**. An increase in ICP or decrease in blood pressure following hypovolaemia impair cerebral blood flow (CBF). **C**. The subsequent decrease in CBF reduces metabolic processes decreasing cerebral oxygen deliver. These pathologies impair the neuronal electric activity, then ability to maintain the resting membrane potential and initiation of the active membrane potential. **D**. A decrease in CBF below 10 mL 100 g^{-1} tissue per min definitely inhibits neuronal metabolism leading to neuronal death

for cognitive dysfunction after TBI as it is markedly decreased in TBI patients with cognitive impairment [60]. In an experimental study, oral supplementation of citric acid reduced lipid peroxidation, inhibited neuroinflammation, TNF-α and nitrate production in Swiss male albino mice brains [61]. Nevertheless, citrate is a derivative of citric acid and its effect on brain metabolisms requires further study.

IMPORTANCE OF DAILY AND CUMULATIVE FLUID BALANCE

A cumulative fluid balance has been proposed as one of the most important factors affecting outcome in patients treated for TBI (Fig. 1). Insufficient fluid administration in the early phase of TBI may lead to cerebral hypoperfusion or intensify brain oedema. Excessive fluid administration in the presence of a leaky BBB may lead to refractory intracranial hypertension while aggressive fluid removal and negative fluid balance may result in AKI [62]. Many clinicians still believe in the beneficial effects of a negative fluid balance in TBI patients, which can be achieved by high dose diuretics. However, uncontrolled use of diuretics together with mannitol has been associated with a high incidence of AKI and increased risk of worse outcomes or death in TBI patients [62, 63]. Several studies have also documented that a fluid balance lower than 0.5–0.8 L during 96 hours post-TBI is independently associated with poor outcomes [62, 64]. Mannitol intensifies extraction of water, Na^+ and other electrolytes via osmotic diuresis leading to temporary hyponatremia in TBI [63]. Diuresis-related hyponatremia reduces blood tonicity and escalates the outflow of Na^+ from BISF. An excessive forced diuresis and the use of hypotonic solutions may intensify this process. Interestingly, 54.9% of neurointensivists prefer hypertonic saline in the early phase of TBI while 45.2% of them prefer mannitol [65]. The criteria for use of mannitol or hypertonic saline should be guided by plasma osmolality and plasma sodium concentration, while cumulative fluid balance should be a minimal 0.8 L positive during the first 96 hours of treatment.

TONICITY OF FLUID AND TBI-RELATED HYPONATREMIA (SALT-WASTING SYNDROME)

Electrolyte imbalances, especially disturbance in Na^+, are frequently observed in patients with TBI. Hyponatremia (serum sodium concentrations lower than 135 mmol L^{-1}) can occur in patients treated for TBI, subarachnoid haemorrhage (SAH) and after neurosurgical procedures, and is associated with increased mortality [29, 66, 67]. Its pathophysiology has been poorly understood. Two principal causes of TBI-related

hyponatremia have been established, namely: cerebral salt wasting (CSW) and the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) [68, 69]. Fluid status is the main key in differentiating between CSW and SIADH. An inappropriate urinary salt loss associated with hypovolaemia (especially extracellular hypovolaemia) is typical for CSW, while an inappropriate secretion of antidiuretic hormone following increased atrial or brain natriuretic peptides generates SIADH [29, 67–71]. To put it simply, CSW can be diagnosed in hypovolaemic patients with hypotonic hyponatremia (e.g. patients receiving excess hypotonic solutions), whereas SIADH can be defined as hypotonic hyponatremia in an euvolaemic or hypervolaemic patients [72, 73]. Hence, CSW should be treated with sodium and water, whereas SIADH requires sodium supplementation with water restriction [69, 70].

Vasopressin is commonly used as a vasoconstrictive drug. It is the antidiuretic hormone, which is secreted by the posterior pituitary gland following hypovolaemia and a rapid increase in plasma osmolality. Although a decline in plasma sodium concentration was observed 16–24 hours after beginning vasopressin administration, in 16% of the TBI patients hyponatremia developed earlier (2–4 days after injury) and was associated with lesions in the limbic system, presumably resulting in inappropriate vasopressin secretion [67, 74]. Hyponatremia also occurs in more than 10% of patients on the first day of mannitol administration and more than 20% of patients receiving mannitol for 7-days [63, 75]. Persistent hyponatremia leads to osmotic demyelination manifested by seizures, coma, brain oedema, and brainstem herniation in the critical-onset cases.

Hyponatremia may be classified into two subtypes. Hypotonic hyponatremia (hypovolaemic, euvolaemic or hypervolaemic) usually courses with low plasma tonicity, whereas isotonic or hypertonic hyponatremia results from extravasation of osmotically active fluids, such as glucose or mannitol [67]. Hypovolaemic hypotonic hyponatremia frequently develops in patients treated with hypotonic fluids and loop diuretics [76, 77]. The use of "in vivo" hypotonic solutions intensifies renal fluid losses and stimulates vasopressin secretion, which can be particularly unfavourable in TBI patients with lesions in the limbic system [67, 74, 76, 77].

Electrolyte-free fluids should be avoided in patients with euvolaemic or hypervolaemic hyponatremia, while the administration of isotonic or hypertonic saline is recommended for the treatment of hypovolaemic hyponatremia [67, 73, 77]. Patients with TBI complicated by severe hypovolaemic hyponatremia require an increase in serum Na^+ concentration at the rate ' 1 mmol L^{-1} per hour with strictly controlled haemodynamic parameters, such as stroke volume variation (SVV), cardiac index (CI) and central venous pressure (CVP). Additionally, plasma and urine osmolality, as well as electrolyte concentrations should be monitored to correct the electrolyte imbalance during continuous high-dose sodium administration. All hypotonic solutions are strongly contraindicated while hypertonic saline with the concomitant administration of furosemide are recommended to minimize the risk of volume overload. However, the administration of sodium may increase Na^+ extraction with urinary water *per se* in some patients with the cerebral salt wasting syndrome. Such patients require corticosteroids administration [73, 77].

CONCLUSIONS

In conclusion, although balanced crystalloids are sometimes preferred over normal saline in patients treated for TBI, there is inadequate evidence on which to base a recommendation. Those preferring a balanced crystalloid have to choose from a variety of cationic and anionic recipes. The most rational would be one of the bicarbonate dialysis solutions in order to avoid untested and unphysiological anions. Hypotonic solutions buffered with citrate should be avoided in patients with TBI. Fluid therapy must be monitored by plasma osmolality and plasma sodium concentrations.

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Manu L.N.G. Malbrain is founding President of WSACS (The Abdominal Compartment Society) and current Treasurer, he is also member of the medical advisory Board of Pulsion Medical Systems (part of Maquet Getinge group) and consults for ConvaTec, Acelity, Spiegelberg and Holtech Medical. He is co-founder of the International Fluid Academy (IFA). This article is endorsed by the IFA. The mission statement of the IFA is to foster education, promote research on fluid management and hemodynamic monitoring, and thereby improve the survival of the critically ill by bringing together physicians, nurses, and others from throughout the world and from a variety of clinical disciplines. The IFA is integrated within the not-for-profit charitable organization iMERiT, International Medical Education and Research Initiative, under Belgian law. The IFA website (http://www.fluidacademy.org) is now an official SMACC affiliated site (Social Media and Critical Care) and its content is based on the philosophy of FOAM (Free Open Access Medical education — #FOAMed). The site recently received the HONcode quality label for medical education (https://www.healthonnet.org/HONcode/Conduct.html?HONConduct519739).

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