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# Fluid therapy in neurotrauma: basic and clinical concepts

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## Abstract

**The patient with head trauma is a challenge for the emergency physician and for the neurosurgeon. Currently traumatic brain injury constitutes a public health problem. Knowledge of the various therapeutic strategies to provide support in the prehospital and perioperative are essential for optimal care. Rapid infusion of large volumes of crystalloids to restore blood volume and blood pressure quickly is now the standard treatment for patients with combined TBI and HS The fluid in patients with brain and especially in the carrier of brain injury is a critical topic; we present a review of the literature about the history, physiology of current fluid preparations, and a discussion regard the use of fluid therapy in traumatic brain injury and decompressive craniectomy.**

## Keywords

*Brain trauma; Colloid solutions; Fluid resuscitation*

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## Introduction

Traumatic brain injury (TBI) is a major public health problem and a leading cause of death and disability [1]. It is frequently accompanied by hemorrhagic shock (HS) [2-5]. The mechanism for adverse outcome in patients with combined TBI and HS may be due in part to secondary ischemic injury to the already vulnerable brain following loss of cerebral auto-regulation and/or to adverse effects of TBI itself on the normal compensatory response to HS [6]. Rapid infusion of large volumes of crystalloids to restore blood volume and blood pressure quickly is now the standard treatment for patients with combined TBI and HS [7,8]. Perioperative fluid administration is an important aspect of surgical care, but is often poorly understood [9-13], and continue to be an exercise in empiricism, with nagging questions about efficacy and complications [14].

Fluid therapy (FT), as the name implies is a treatment with fluids, thus, is a drug [15]. The final goal of fluid management is to optimize the circulatory system to ensure the sufficient delivery of oxygen to organs [16]. FT is needed for the following requirements:

1. Normal maintenance;
2. Blood or fluid loss (wounds, drains, induced dieresis, etc);
3. "Third space losses" (fluid sequestration in tissue edema or ileus); and
4. Increased systemic requirements due to fever and hypermetabolic state.

TF should be tailored to match these requirements [17]. Intravenous (IV) fluids may broadly be classified into colloid and crystalloid solutions. They have very different physical, chemical, and physiological characteristics. Colloid solutions can be natural (albumin) or synthetics (gelatins, dextranes, and hydroxyethyl starches).

Goal-directed fluid therapy (GDT) aimed at optimizing cardiac output and oxygen delivery has been shown to improve outcome for high-risk surgical patients [18]. The majority of the information presented here is derived from the fluid management for the surgical patient in general, and those critically ill, such as trauma patient. Primary studies on preoperative fluid therapy for DC are sparse.

The fluid management for patients undergoing elective major surgery, e.g., neurotrauma surgery, is controversial [19-21]. During the perioperative period, many pathophysiological changes occur that alter the normal efficiency of fluid homeostasis. Despite this, perioperative fluid prescription is often poor, being based on an insufficient knowledge of water and electrolyte requirements and distribution [22-25]. Perioperatively, crystalloids, colloids and blood components are required to meet the ongoing losses and for maintaining cardiovascular stability to sustain adequate tissue perfusion [26,27].

Intravenous fluids maintain hydration while patients are unable to drink and replace losses that occur as a result of surgery [28]. Severity of illness, magnitude and duration of surgery, comorbidities and the host response to injury, influence the perioperative fluid needs. Although the principle goal of fluid administration is to maintain adequate tissue perfusion and the perils of over and under-resuscitation are well documented, there are no standards of care guiding perioperative fluid administration [28]. The aim of this work is to review current topics of fluid management in the patients with traumatic brain injury and those who are candidate to decompressive craniectomy.

## History of modern fluid therapy

IVF first gained therapeutic importance in the treatment of cholera in the 1830s [29-34], with the reports of William Brooke O'Shaughnessy about his terminal cholera patients' blood observations [29]. Their blood were "thick and obscure", thus concluding there was water deficit in those patients [31]. Aiming to replace the corporal fluid loses was prepared the misnamed 0.9% physiologic saline solution for surgical patients.

From the 1880s, IVF began to be administered perioperatively to compensate for the "injurious" effects of anesthesia. Clinical improvements were consequently noted, though the adverse effects of saline were observed. Thomas Latta was the first to administrate intravenously water and salt solutions to dying patients with no great results [29,35]. Water and salt solutions were randomly mixed and in conjunction with the poor hygienic practices of those times, the FT initially wasn't firmly instituted [15].

In 1880, Sidney Ringer observed the different protoplasmic activity of sodium, calcium, potassium and chloride salts, and originating "Ringer's solution" [15]. George Crile in 1899, with a hemorrhagic shock animal model, studied the reanimation, recommend it in warm way. In the First World War, took place treatments of war injuries with primitive saline and colloid solutions. The Gum Arabic, a natural colloid from the *Acacia senegalis* tree used by W.C. Cannon, was a highlighted colloid [15].

In 1924, the intravenous "drip" was introduced by Rudolph Matas. In 1930, Hartmann and Senna looking for evading the hyperchloremic acidosis derived from the use of Ringer´s solutions [36], added sodium lactate, allowing sodium to be linked to the excess of chloride, facilitating the lactate metabolism, and thus, giving origin to the Hartman solution or Ringer-lactate. The work of Ringer, Hartmann, and others emphasized the importance of the composition of IV fluids and laid the foundations for the balanced solutions in use today [37]. During the Second World War, blood and plasma were massively administrated, even in the battlefield, with the aim to enhance injured soldier surviving. In general, FT has been continuously in change, depending on current trends [15]. As the metabolic response to injury was increasingly investigated in the 1940s and 1950s, the cause of post-operative oliguria was debated widely with the most prominent surgeons being Moore and Shires [37]. During Vietnam War, the preservation of renal function, becomes a therapeutic objective, thus, were protocolized the use of large amounts of crystalloid for the hemorrhagic shock in the Da Nang Army Hospital. In this moment, took place the observations of pulmonary complications derived from those large volumes of fluids, generating the "Da Nang lung", "wet lung syndrome", previous denominations of the today Adult Respiratory Distress Syndrome (ARDS).

These differences in opinion, coupled with reports of injured soldiers from the Korean War receiving large IV fluid infusions and surviving, dictated the surgical practice of liberal IV fluid administration until very recently [37]. Newer work in fluid therapy has explored the concept of fluid restriction. Shoemaker and colleagues also pioneered the concept of fluid administration to achieve supranormal indices of cardiorespiratory function, which has led to the advent of goal-directed fluid therapy [37]. Alongside the development of balanced solutions, the renewed focus on perioperative fluid therapy has led to IVF administration being guided by physiological principles with a new consideration of the lessons gleaned from history [37]. With military medicine advances, fluid therapy is going catching more, and more attention, being important to receive fluid therapy plus hemotherapy, but, with no clear ideas about the proper volume. Currently, fluid therapy stills with large controversies.

## Fluid physiology

The fundamentals governing fluid and electrolyte management in patients date to the 19th century [38]. In the first half of the 20th century work by Gamble and Darrow and colleagues defined the electrolyte content of extracellular, intracellular and interstitial fluid compartments [38]. 60% of the human adult body is composed by water, two-thirds of this is intracellular water, and the remaining third is the extracellular compartment, which in turn is divided between intravascular and extravascular or interstitial compartments [39,40]. The interstitial compartment is actually a matrix, a collagen/gel substance that allows the interstitium to provide structural rigidity which resists gravity and can maintain structural integrity during extracellular volume depletion. The collagen/gel interstitial space,

especially in skin and connective tissue, is an important reservoir of extracellular fluid [38]. The total intravascular volume, also referred as blood volume, has approximately 5 l and has intracellular (red and white cells and platelets: 40%; 2 l) and extracellular (plasma: 60%; 3 l) components [39,40]. Extracellular compartment is important for oxygen and nutrients transport, and the elimination of carbonic anhydride and other products from cellular metabolism. There is another compartment, the transcellular, which is composed by fluids not equilibrated with the other fluids, and it is constituted by synovial, cerebrospinal fluids, gastrointestinal secretions, etc. This compartment through the lymphatic system returns the fluids to the intravascular space [40].

The cells and the intravascular space have membranes that preserve their structural integrity and allow the molecule and fluid interchange between different compartments. The main objective of membranes is preserve osmolarity and the electronegativity of each one of the compartments. The cell wall separates the intracellular compartment from the extracellular compartment. The capillary endothelium and the walls of arteries and veins divide the extracellular compartment into the intravascular and the interstitial (tissue or extravascular) compartments. Water moves freely through cell and vessel walls and is distributed throughout all these compartments. The energy-dependent Na/K adenosine triphosphatase in cell walls extrudes Na+ and Cl- and maintains a sodium gradient across the cell membrane: Na+ is an extracellular ion. The capillary endothelium is freely permeable to small ions such as Na+ and Cl-, but is relatively impermeable to larger molecules such as albumin and the semisynthetic colloids, e.g., gelatins and starches, which are therefore normally theoretically maintained in the intravascular space. Plasma is a solution in water of inorganic ions (predominantly sodium chloride), simple molecules such as urea, and larger organic molecules such as albumin and the globulins. Plasma volume and interstitial fluid volume is highly exchangeable. Fluid exchange through a capillary is regulated by Starling's law, which mathematically summarizes the forces governing the flow of fluid out of blood vessels into surrounding tissues, states that:

$$Qf = Kf \times [(Pc - Pi) - R(\pi c - \pi i)]$$

Where Qf is the total fluid flux out of capillaries (not represent the quantity, but just the speed of water movement [16]) and Kf is the filtration coefficient (the product of the membrane conductance and the membrane surface area), Pc is intravascular hydrostatic pressure, Pi is interstitial hydrostatic pressure, $\pi c$ is colloid osmotic pressure within the vasculature, $\pi i$ is interstitial colloid osmotic pressure gradient across the vessel wall, and R is the oncotic reflection coefficient, the tendency of a membrane to impede the passage of oncotically active particles [16,41].

A R of 0 indicates a membrane that is totally permeable to protein while a R of 1 indicates a membrane that completely prevents protein diffusion. Distribution terminates when the balance of the hydrostatic pressure and the osmotic pressure cancel each other out. Because the interstitium consists not only of free space but also of absorbent gel, captured water in the gel does not contribute to lowering the osmotic pressure in the interstitium [16]. Therefore, the osmotic pressure does not easily change until the gel is saturated by water movement. This is a mechanism of edema formation. Thus, Starling's law does not determine the distribution ratio between plasma and interstitium, it just explains the movement of water through the capillary wall [16].

The original interpretation of an equilibrium including fluid re-absorption at the venous end of the microcirculation is now known to be incorrect through actual measurement of the pressures involved. Rather, a steady state is involved, with a level of permeability to plasma proteins in the microvascular walls. Net fluid movement occurs in the vessels from the intravascular to the perivascular components [42]. The fluid transfer is mediated by the endothelial glycocalyx layer (EGL), a physiological entity discovered and studied over the past 30 years [43]. A model for fluid transfer across the EGL [44] accounts for the discrepancies observed in fluid transfer as predicated by Starling's original equation,

and proposes a modified hypothesis based on pressures involving the generation of fluid through the glycocalyx rather than the interstitial space [45] modifying the Starling equation to:

$$Qf = (Pc - Pi) - R \times (\pi c - \pi g)$$

Where Pi and πg are the hydrostatic and osmotic pressures, respectively, exerted by the ultrafiltrate formed across the glycocalyx [46]. While the EGL is the conduit for water passage from the intravascular to the extravascular space, plasma proteins cross the endothelial barrier through a separate pathway, the large pore system [46]. This model is perturbed by a number of factors during anesthesia and surgery. Patients present for surgery with a variety of conditions that result in altered fluid distribution. Many anesthetic drugs (e.g., IV induction drugs and volatile anesthetics) cause vasodilation, leading to a reduction in the ratio between the circulating volume and the capacity of the intravascular space, or myocardial impairment, leading to a reduction in flow through the circulation. Fluid shifts between compartments may also reduce the circulating volume (third-space losses and loss of intravascular fluid into the interstitium because of altered endothelial permeability in sepsis and inflammatory states) [39]. In the next items, it will be presented a resume of the main characteristics of different kind of solutions.

## Crystalloids

A crystalloid fluid is a solution of small water-soluble molecules that can diffuse easily across semipermeable membranes. The properties of these solutions are largely determined by their tonicity (osmolality relative to plasma) and their sodium content (affecting their distribution within body compartments) [47]. They redistribute throughout the ECF compartment, of which 75% is interstitial fluid. This suggests that 4 liters of crystalloid are required to replace a blood loss of 1 liter [48]. Studies have shown that the volume kinetics of infused crystalloid solutions differ between normovolemic and hypovolemic patients [49].

IV infusions of isotonic saline solution only expand the intravascular space by a maximum of one-third of the volume used in normal subjects, with only 16% left after 30 minutes. The volume of crystalloid required to replace an acute blood loss remains 3-4 fold because of redistribution into, and rapid elimination from, the ECF [48].

### Isotonic solutions

Isotonic or iso-osmolar solutions, with an osmolality ≈ 300 mOsm/l, such as sodium chloride 0.9% (normal saline), Ringer's solution or plasmalyte, do not change plasma osmolality and do not increase brain water content [50]. They also contain sodium at physiological plasma concentrations. These fluids distribute freely within the extracellular fluid (ECF) compartment causing little change in sodium concentration and osmolality. As a result this limits the movement of water out of the ECF into the ICF compartment and *viceversa*. Commercial lactated Ringer's solution is not truly iso-osmolar with respect to plasma. 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 [50].

### Hypotonic solutions

Large amounts of hypo-osmolar or hypotonic fluids reduce plasma osmolality, drive water across the BBB, and increase cerebral water content and ICP. 5% 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 [50]. As a consequence, hypo-osmolar crystalloids (0.45% NaCl or D5W) should be avoided in neurosurgical patients [50].

### Hypertonic crystalloids: mannitol and hypertonic saline

Osmotherapy agents such as hypertonic saline (HTS) are currently being used in the treatment of patients with post-traumatic cerebral edema and raised intracranial pressure (ICP) resulting from TBI [51]. It's said to have a particularly useful role for the treatment of ICP whilst administering small volume fluid resuscitation [52]. HTS solutions typically improve cardiovascular output as well as cerebral oxygenation whilst reducing cerebral edema. Hypertonicity seems to affect some innate immune-cell functions, specifically neutrophil burst activity in preclinical studies, probably this could have beneficial effects on modulation of the inflammatory response to trauma [53-58].

Clinical studies however do not provide compelling evidence to support the use of HTS either for TBI or for hemorrhagic shock. One small RCT (n = 222) reported a significant reduction in mortality when comparing a 250 ml bolus of HTS/dextran with isotonic saline in 222 patients with hemorrhagic shock [59]. But many other RCTs have not demonstrated mortality benefit in this group of patients [60-63], including the most recent and largest RCT comparing HTS, HTS/dextran and normal saline. This trial recruited two separate cohorts, one with TBI (n = 1087) [64] and one with hemorrhagic shock (n = 853) [65]; with primary endpoints of neurological outcome at 6 months after TBI and 28 day survival, respectively. The TBI study was terminated early due to futility, as interim analysis was unable to demonstrate an improvement in neurological status or indeed mortality at 6 months. The second study demonstrated no significant difference in mortality at 28 days, and was terminated early for concerns of potential (albeit statistically non-significant) increase in mortality observed with a subgroup of patients receiving HTS but no blood transfusions within the first 24 h [65].

Wade et al. [66] undertook a cohort analysis of individual patient data from a previous prospective randomized double-blinded trial to evaluate improvements in survival at 24 hours and discharge after initial treatment with HSD in patients who had TBI (head region Abbreviated Injury Score ≥4) and hypotension (systolic blood pressure ≤90 mm Hg). Found that treatment with HSD resulted in a survival until discharge of 37.9% (39 of 103) compared with 26.9% (32 of 119) with standard of care ($p = 0.080$). Using logistic regression, adjusting for trial and potential confounding variables, the treatment effect can be summarized by the odds ratio of 2.12 ($p = 0.048$) for survival until discharge. They conclude that patients who have traumatic brain injuries in the presence of hypotension and receive HSD are about twice as likely to survive as those who receive standard of care.

Rockswold et al. [67] examined the effect of hypertonic saline on ICP, cerebral perfusion pressure (CPP), and brain tissue oxygen tension ($PbtO_2$), and found that hypertonic saline as a single osmotic agent decreased ICP while improving CPP and $PbtO_2$ in patients with severe traumatic brain injury. Patients with higher baseline ICP and lower CPP levels responded to hypertonic saline more significantly.

## Colloids

Colloids are fluids with larger, more insoluble molecules that do not readily cross semi-permeable membranes, across which they exert oncotic pressure. Water is drawn in from the interstitial and ICF by osmosis. Their movement out of the intravascular space and their duration of action depend on their molecular weight, shape, ionic charge and the capillary permeability [47]. Apart from albumin, all colloids are polymers and contain particles with a range of molecular weights [48]. They may increase plasma volume by more than the volume infused because of their higher osmolality; hence the term plasma expanders [48]. Studies suggest they can cause significant impairment of clot formation activity [68,69].

### Albumin

Albumin is a multifunctional, non-glycosylated, negatively charged plasma protein, with a molecular weight of 69 kD. Albumin is a biological therapeutic, manufactured from an inherently variable source

material using a variety of purification techniques. Albumin is an effective volume expander, has not been associated with allergic-type reactions, and has no intrinsic effects on clotting [50]. Its use as reanimation fluid has not been linked to better surviving in compared with the synthetic colloids, fact that together with costs, discredits its use in critically ill patients [70]. There are different concentrations: iso-oncotic (4-5% albumin) and hyper-oncotic (20% albumin). The later has adverse renal events.

## Sintetic colloids

### Gelatins

Gelatin products are semi-synthetic colloids derived from bovine collagen and prepared as polydispersive solutions by multiple chemical modifications [48,71]. Gelatins for volume therapy have been withdrawn from the US market due to the high rate of anaphylactic reactions [71]. Conventional gelatin preparations have a mean molecular weight of 30-35kDa and a low molecular mass range. Their intravascular persistence is short (2-3 hours), particularly for the urea-linked gelatins, which are excreted rapidly renally (80% molecules < 20 kDa). Since the cross-linked gelatin molecules contain negative charges, chloride concentrations of the solvent solution are reduced in contrast to other types of colloid. Since the latter fact results in slight hyposmolality, infusion of large amounts of gelatin solutions may reduce plasma osmolality and ultimately foster the genesis of intracellular edema [71]. The rapid urinary excretion of gelatin is associated with increased diuresis and has to be substituted by adequate crystalloid infusion to prevent dehydration. Gelatin infusion may furthermore increase blood viscosity and facilitate red blood cell aggregation without influencing the results of crossmatching.

Severe anaphylactoid reactions are low (though more likely with gelatins than with other colloids), and usually occur only with rapid infusions (1/13000 for succinyl ated gelatin; 1/2000 for urea-linked gelatin), though much less with newer formulations. Reactions are usually mild (incidence < 0.4%) [48]. Clinically, they have little effect on coagulation [48].

### Dextranes

These are neutral, high-molecular-weight glucopolysaccharides based on glucose monomers. Dextranes are derived from the action of the bacterium *Leuconostoc mesenteroides* on a sucrose medium via the dextran sucrose enzyme. This produces a group of branched polysaccharides of 200,000 glucose units. Subsequent partial hydrolysis produces molecules of mean MW 40, 60, 70 and 110 kDa, with half-lives ranging from 15 minutes to several days. They are mainly excreted via the kidneys (70%), with the rest metabolized by endogenous dextranase. They are relatively cheap (4-5 £/500 ml).

Dextran 40 is hyperoncotic and initially acts as a plasma expander before its rapid elimination by the kidney. Its main use is in promoting peripheral blood flow (e.g. in prophylaxis for deep vein thrombosis and arterial insufficiency). Dextran 70 and 110 are mainly used for plasma expansion; 6% dextran 110 is no longer available clinically. Improvement in blood flow results from a reduction in blood viscosity, possibly by coating the vascular endothelium and cellular elements of blood, thus reducing their interaction. Dextrans inhibit platelet adhesiveness, enhance fibrinolysis and may reduce factor VIII activity. Doses above 1.5 g/kg produce a bleeding tendency. Initial use should be limited to 500-1000 ml with a restriction of 10-20 ml/kg/day thereafter.

Modern solutions do not interfere with blood cross-matching or cause roleaux formation, which was a feature of the early, very high MW dextrans. They can impair renal function by tubular obstruction from dextran casts. This is usually seen with dextran 40 combined with hypovolaemia and pre-existing renal dysfunction. They can also cause an osmotic diuresis. Severe anaphylactic reactions can occur (immune complex type III), resulting from prior cross-immunization against bacterial antigens forming dextran-reactive antibodies. The incidence of 1/4,500 is reduced with monovalent hapten pre-treatment (injection of 3 g dextran 1) to 1/84,000. This blocks the antigen-binding sites of circulating antidextran antibodies, preventing formation of immune complexes with subsequent infusions of dextran 40 or 70 [48].

### Hydroxyethyl starch

HES was used extensively to treat wounded soldiers during the Vietnam War [71]. HES are semi-synthetic colloids related to glycogen. The raw material for the production of HES is amylopectin, a highly branched polymer of glucose, derived from either waxy-maize or potato starch [71], which are etherified with hydroxyethyl groups into the D-glucose units. HES has a much lower viscosity than dextran or gelatin, but does not reach the low viscosity of albumin. The mean molecular weight of the different HES preparations ranges between 70 and 670 kDa. Following infusion of HES, small molecules <60 kDa are filtrated into the urine, whereas larger molecules are degraded by plasma amylase.

The kinetics of this degradation are mainly determined by the molar substitution and the C2/C6 ratio (i.e. the quotient of the numbers of glucose residues hydroxyethylated at positions 2 and 6, respectively) [71]. A high molar substitution and a high C2/C6 ratio make the HES molecule less susceptible to plasma amylase, and thus increase the intravascular half-life of HES molecules. Part of the HES is stored within the reticulo-endothelial system and slowly degraded to $CO_2$ and water [71].

However, massive infusion of old, high-molecular-weight preparations with a high degree of substitution (particularly heta- and hexastarch) may be associated with excessive tissue storage. With modern preparations (i.e. 6% HES 130/0.4), no plasma accumulation and greatly reduced tissue storage have been reported in the literature [71]. The reduction in viscosity of HES solutions results from the globular structure associated with the high degree of branching [71].They are classified as shown in Table 1. They are hydrolyzed to smaller molecules by amylase and renal elimination is rapid for polymers over 50 kDa. The action of amylase is suppressed by higher degrees of substitution and with greater etherification at the C2 versus C6 position. Intravascular half-life is thus maximized especially when the initial MW is high. As well as persistent plasma expansion, HES plug capillary leaks induced by sepsis and major trauma and restore macrophage function after hemorrhagic shock. Compared with 20% albumin in these patients, 10% HES significantly improves hemodynamic parameters in the systemic and microcirculation (splanchnic perfusion) [48].

## Fluid therapy and traumatic brain injury

Clinically acceptable fluid restriction has little effect on edema 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 [72]. Thus the old concept of benefit from fluid restriction was simply a consequence of an increased osmotic gradient over time [50].The available data indicate that volume replacement and expansion will have no effect on cerebral edema 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. As previously mentioned, 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) [50].

| | |
|---|---|
| **MWw [kDa]** | High (450–480);<br>Medium (130–200);<br>Low (40–70) |
| **Degree of substitution** | High (0.6–0.7);<br>Low (0.4–0.5) |
| **C2:C6 ratio** | High > 8;<br>Low < 8 |
| **Concentration** | High 10%;<br>Low 6%. |

**Table 1.** Classification of hydroxyethyl starch preparations

In TBI, a blunt or penetrating injury incites mechanical and autodigestive destruction of the normally tightly intact endothelium of the blood brain barrier [73]. This allows uncontrolled

movement of fluid and serum proteins into the brain parenchyma, eventually leading to vasogenic cerebral edema and increased ICP. It has been shown that in critically ill patients, there is increased leakage of albumin across the capillary wall [74]. In the brain, this increased extravasation of albumin could lead to increased interstitial oncotic pressure and exacerbate cerebral edema.

## Pre-hospital

In nine randomised controlled trials and one cohort study of pre-hospital fluid treatment in patients with TBI [75], hypertonic crystalloids and colloid solutions were not more effective than isotonic saline [76]. In a combined polytrauma model of uncontrolled hemorrhage and TBI in swine, Teranishi et al. [6] investigated if pre-hospital administration of the hemoglobin based oxygen carrier HBOC-201 will improve tissue oxygenation and physiologic parameters compared to LRsolution. They found that mean TBI force (2.4 ± 0.1 atm; means ± standard error of the mean) and blood loss (22.5 ± 1.7 ml/kg) were similar between groups. Survival at the 6h endpoint was similar in all groups (≈50%). Cerebral perfusion pressure (CPP) and brain tissue oxygen tension were significantly greater in HBOC-201 as compared with LR animals ($p < 0.005$). Mean arterial pressure (MAP) and mean pulmonary artery pressure (MPAP) were not significantly different amongst groups. Blood transfusion requirements were delayed in HBOC-201 animals. Animals treated with HBOC-201 or LR showed no immunohistopathological differences in glial fibrillary acidic protein (GFAP) and microtubule-associated protein 2 (MAP-2). Severity of subarachnoid and intraparenchymal hemorrhages were similar for HBOC and LR groups. They conclude that in their polytrauma swine model of uncontrolled hemorrhage and TBI with a 30 minute delay to hospital arrival, pre-hospital resuscitation with one bolus of HBOC-201 indicated short term benefits in systemic and cerebrovascular physiological parameters. True clinical benefits of this strategy need to be confirmed on TBI and hemorrhagic shock patients.

## In-hospital

A defined strategy for volume replacement and fluid balance that includes maintenance of normovolemia and colloid osmotic pressure in combination with a neutral to a slightly negative fluid balance is a cornerstone of the intracranial pressure ICP-targeted therapy for severe TBI [77]. In contrast to hemorrhage and hemorrhagic shock, possibilities for life-saving interventions are very limited in CNS injury. The significant contribution of HS to brain injury mortality further illustrates the role of hemorrhage control in reducing mortality in trauma patients [78].

Crystalloid resuscitation should be targeting a corridor of safety, avoiding both extremes of overt hypovolaemia and fluid overload. While avoidance of edema formation is a prime objective and concern in visceral surgery, efforts to restrict fluids, such as forced hypovolaemia, are associated with oliguria and occasionally renal shutdown, and may impair nutritional microvascular blood flow in other vascular beds such as the splanchnic circulation. Fluid excess, on the other hand, is presumably a cause of perioperative morbidity and mortality [79]. Sequelae of volume overload are particularly well known, and the pathophysiological cascades of events have been worked out best for the patient with aggressive crystalloid resuscitation after major trauma. Manifestations of crystalloid overload might include ARDS and brain edema in the patient with concomitant head injury [80-84].

Wahlström et al. [77] analyzed the occurrence of organ failure and mortality in patients with severe TBI treated by a protocol that includes defined strategies for fluid therapy (albumin administration to maintain normal colloid osmotic pressure and advocates a neutral to slightly negative fluid balance). Ninety-three patients with severe TBI and Glasgow Coma Scale ≤ 8 were included during 1998-2001. Medical records of the first 10 days were retrieved. Organ dysfunction was evaluated with the Sequential Organ Failure Assessment (SOFA) score. Mortality was assessed after 10 and 28 days, 6 and 18 months. They found that the total fluid balance was positive on days 1-3 and negative on days 4-10. The

crystalloid balance was negative from day 2. The mean serum albumin was 38 ± 6 g/l. Colloids constituted 40-60% of the total fluids given per day. Furosemide was administered to 94% of all patients. Severe organ failure defined as SOFA ≥ 3 was evident only for respiratory failure, which was observed in 29%. None developed renal failure. After 28 days, mortality was 11% and, after 18 months, it was 14%. Thus, a protocol including albumin administration in combination with a neutral to a slightly negative fluid balance was associated with low mortality in patients with severe TBI in spite of a relatively high frequency (29%) of respiratory failure, assessed with the SOFA. Acute lung injury (ALI) and ARDS are reported commonly after TBI and their appearance is associated with fluid management. ALI and ARDS are considered as independent factors for mortality [85-88].

A single equimolar infusion of 7.45% hypertonic saline solution is as effective as 20% mannitol in decreasing ICP in patients with brain injury [79]. In the Taiwan guidelines for TBI management, when it is needed massive fluid transfusion, recommends that normal saline is better than lactated Ringer's solution (grade D). Fresh frozen plasma is only indicated for coagulopathy and not recommended to be used as a regular volume expander (grade C). Hypertonic saline may be useful in patients who have complication of severe TBI and systemic shock (grade D) [89].

The Saline versus Albumin Fluid Evaluation (SAFE) study was an international trial that randomized critically ill patients to either 4% albumin or normal saline fluid resuscitation for 28 days [89]. Although there was no overall difference in 28-day mortality between the 2 groups, there was a trend toward increased mortality in patients with trauma randomized to albumin resuscitation. This increased mortality appeared to be driven by patients with trauma with TBI compared with those patients with trauma without TBI. A post hoc analysis of patients with TBI randomized during the SAFE study confirmed that resuscitation with albumin was associated with increased mortality at 24 months when compared with normal saline [90,91]. This increased risk was entirely driven by patients with severe TBI, defined as GCS ≤ 8.

Sekhon et al. [91] in their study (n=171) looking for determine if there is an association between synthetic colloids and mortality in patients with severe TBI, found that patients receiving pentastarch had higher Acute Physiology and Chronic Health II scores (23.9 vs. 21.6, $p < 0.01$), frequency of craniotomy (42.5% vs. 21.6%, $p = 0.02$), longer duration of intensive care unit stay (12 vs. 4 days, $p < 0.01$), and mechanical ventilation (10 vs. 3 days, $p < 0.01$). On unadjusted Cox regression, patients in the highest quintile of cumulative pentastarch administration had a higher rate of mortality compared with those receiving no colloid (HR = 3.8; CI95% = 1.2-12.4; $p = 0.03$]. However, this relationship did not persist in the final multivariable model [HR = 1.0; CI95% = 0.25-4.1; $p = 0.98$]. They conclude that there was no association between cumulative exposure to pentastarch and mortality in patients with severe TBI.

Elliot et al. [51] in a study focused on the hypothesis that hypertonic saline-induced improvements in histological outcome are time dependent and may be associated with alterations in astrocyte hypertrophy after cortical contusion injury, examined histopathological changes at 7 days after controlled cortical impact (CCI) injury in a rat model. They found that hypertonic saline treatment reduced tissue loss that correlated with attenuated astrocyte hypertrophy characterized by reductions in astrocyte immunoreactivity without changes in the number of astrocytes after CCI injury. Delayed treatment of hypertonic saline resulted in the greatest reduction in tissue loss compared to all other treatments (0.9% normal saline – NS, n = 12; 7.5% hypertonic saline – HS, n = 15; delayed NS, n=3; delayed HS, n=4; or no treatment – CCI control, n=18) indicating that there is a therapeutic window for hypertonic saline use after TBI.

### Hypertonic/hyperoncotic solutions

Recently, attention has been directed at hypertonic/hyperoncotic solutions (typically hypertonic hetastarch or dextran solutions). Because of the hemodynamic stabilizing properties of these fluids in hypovolaemic shock, administration in patients with trauma and TBI might be particularly advantageous for the prevention of secondary ischemic brain damage. Small volumes of such solutions

can restore normovolaemia rapidly, without increasing ICP. They have been successfully used to treat intracranial hypertension in TBI patients [66], and in others neurosurgical acute emergencies (SAH [92] and stroke [93]).

## Fluid therapy for decompressive craniectomy

Some general principles of enhanced recovery fluid management and recommendations of the enhanced recovery partnership [94]:

Pre-operative:

- Maintain good pre-operative hydration;
- Give carbohydrate drinks;
- Avoid bowel preparation.

Perioperative:

- Use fluid management technologies to deliver individualized goal directed fluid therapy;
- Avoid crystalloid excess (salt and water overload). Maintenance fluid, if utilized, should be limited to less than 2 ml/kg/h including any drug infusions. The use of isotonic balanced electrolyte solution (e.g. Hartmann's) will minimize hyperchloraemic acidosis.

Post-operative:

- Avoid post-operative i.v. fluids when it is possible;
- Always ask the question; «What are we giving fluids for?»:
  - Maintenance fluid? Push early drinking and eating;
  - Replacement fluid? Consider oral before IV and consider prescribing oral fluids;
  - Resuscitation fluids? Use goal directed fluid therapy.

### Physiological responses during the perioperative phase

In the critically ill, effects of surgery *per se* and its associated changes in the hormonal *milieu interne* are exaggerated by a systemic inflammatory response with development of capillary leak. This leads to difficult to balance losses into the interstitium and frequently visible edema formation. Resulting abnormalities of fluid and electrolyte balance in the critically ill are purposefully or involuntarily influenced, in addition, by nutritional support and measures that affect acid–base homeostasis [79].

Surgery alters fluid balance [39], generates a systemic inflammatory response which increases oxygen consumption, and is associated with increase in cardiac output and oxygen delivery. An inability to meet the metabolic demands of recovery from surgery is associated with increased morbidity and mortality [95]. The stress response to surgery and trauma involves a number of different physiological reactions. Importantly, the renine-angiotensine-aldosterone system is stimulated, leading to increased sodium and fluid retention, decreased urinary output and altered fluid balance. In addition, the activated inflammatory response causes vasodilatation and increased capillary wall permeability [47]. This affects the intravascular duration of fluids given, with increased capillary leak of fluids into the interstitial tissues. As a result, the perioperative period is a time when the body's management of fluids is dramatically altered and needs to be considered carefully when prescribing and giving fluids [47].

## Conclusions

Perioperative fluid therapy continues to be an exercise in empiricism, with nagging questions about efficacy and complications. There are no evidence-based guidelines or standards of care for the management of fluid therapy in patients who will underwent to decompressive craniectomy.

**Question for further research**

Development of an evidence based guidelines or standard of care for the management of fluid therapy in patients who will underwent to decompressive craniectomy.

Knowledge of the properties of the various available IV fluids, and the knowledge of the pathophysiology of endothelial, parenchymal and endocrine alterations which happen in TBI should guide their administration, to reach a good medium which propitiate allow better neurological, morbidity and mortality outcomes.

| The review in brief | |
|---|---|
| Clinical question | To review current topics of fluid management in the patients with traumatic brain injury and those who are candidate to decompressive craniectomy |
| Type of review | Narrative |
| Search of the literature | PubMed |
| Conclusion | Perioperative fluid therapy continues to be an exercise in empiricism, with nagging questions about efficacy and complications. There are no evidence-based guidelines or standards of care for the management of fluid therapy in patients who will underwent to decompressive craniectomy. Knowledge of the properties of the various available IV fluids, and the knowledge of the pathophysiology of endothelial, parenchymal and endocrine alterations which happen in TBI should guide their administration, to reach a good medium which propitiate allow better neurological, morbidity and mortality outcomes. |
| Limitations | The absence of evidence-based guidelines or standards of care |

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