Management of Fluids and Electrolytes

63

Per-Olof Grände and Niels Juul

Recommendations

Level I

There are insufficient data to support a Level I recommendation for a specific fluid therapy in traumatic brain injury (TBI) patients.

Level II

There has been one Level II study (the SAFE-TBI study) supporting the use of normal saline rather than 4% hypotonic albumin in TBI patients.

Level III

There have been several Level III studies supporting the use of albumin in TBI patients.

There are insufficient data to support the use of synthetic colloids in severe TBI.

63.1 Overview

The infusion of plasma volume expanders is essential after a TBI to counteract hypovolaemia. Hypovolaemia increases the risk of compromised circulation in the most injured part of the brain. A recent experimental study on the cat showed that significant hypovolaemia develops rather quickly after a traumatic head injury (Bentzer and Grände 2017).

The support for saline or other *crystalloid* solutions as the main plasma volume expanders in TBI patients is supported by the results of the SAFE-TBI study (The SAFE Study Investigators 2007). This fluid regimen is cheaper than other fluid regimens using albumin or synthetic colloids.

A crystalloid solution is distributed throughout the whole extracellular space of the body, which means that only 20–25% of the volume infused will stay intravascularly and the rest will be relatively quickly distributed to the interstitial space of the body. The maintenance of normovolaemia with saline or other crystalloids therefore means the need for large volumes, resulting in interstitial oedema with potential side effects in terms of increased lung water, greater diffusion distances and an increased risk of compartment syndrome. What may be more important in TBI patients is that distribution of crystalloids will occur also to the brain interstitium, provided the blood–brain barrier (BBB) is disrupted and becomes permeable for small solutes. There is apparently a risk

P.-O. Grände (✉)
Department of Anaesthesia and Intensive Care, Lund University and Lund University Hospital, Lund, Sweden
e-mail: per-olof.grande@med.lu.se

N. Juul
Department of Anaesthesia, Aarhus University Hospital, Aarhus, Denmark
e-mail: d245364@dadlnet.dk

T. Sundstrøm et al. (eds.), *Management of Severe Traumatic Brain Injury*,
https://doi.org/10.1007/978-3-030-39383-0_63

that the use of crystalloids will trigger the development of tissue oedema not only in organs away from the brain but also in the brain itself in TBI patients (Grände 2006; Jungner et al. 2010).

Albumin has a molecular weight of 69 kDa and is the most essential natural plasma protein. In contrast to synthetic colloids, all the molecules are of the same size, are negatively charged and are not degraded to smaller molecules. As will be discussed below, the fact that albumin is not degraded may be an advantage by exerting a more sustained plasma volume expansion, but it may also be a disadvantage if albumin accumulates in the interstitium. Allergic reactions with albumin are rare. The protein concentration in plasma is reduced after a TBI, reflecting increased leakage of plasma proteins to the interstitium—being beyond the recirculation capacity of the lymphatic system (Bentzer and Grände 2017; Haskell et al. 1997). According to the two-pore theory for transvascular fluid exchange (Rippe and Haraldsson 1994), plasma proteins are transferred to the interstitium through the relatively few large pores at the end of the capillary network and in venules, following the fluid stream mainly through convection. The hydrostatic pressure is the dominating force in the large pores, as the transcapillary oncotic absorbing force is significantly reduced across these pores. This means that even in the normal state, there is a continuous leakage of plasma and plasma proteins from the intravascular space to the extravascular space through these pores, but the capacity of the recirculating lymphatic system is large enough to prevent hypovolaemia and tissue oedema. The loss of plasma fluid is dependent on the number of large pores and on the magnitude of the force of the hydrostatic pressure. This means that there is a risk that the more albumin infused to compensate for hypovolaemia, the more leakage of plasma fluid there will be. Thus, the use of albumin as plasma volume expander should include measures that reduce the transcapillary leakage to volumes below the capacity of the lymphatic system. According to physiological principles of transcapillary fluid exchange as described by the two-pore theory, leakage of plasma fluid to the interstitium can be reduced by maintaining the hydrostatic capillary pressure low. This can be accomplished by avoiding high arterial pressures and avoidance of vasopressors such as noradrenaline (Dubniks et al. 2007; Nygren et al. 2010). The leakage can also be reduced using low infusion rates (Bark and Grände 2014) and higher concentrations of the albumin solution. Physiotherapy may also reduce the need for albumin by stimulating the lymphatic drainage system. As discussed below, the need for albumin infusions may also be reduced by avoidance of low haemoglobin concentrations.

By increasing the plasma oncotic pressure, albumin may induce absorption of fluid from the brain, provided BBB is permeable to small solutes (Tomita et al. 1994; Grände 2006; Jungner et al. 2010). This regime may be questioned if the BBB is disrupted to a large extent, resulting in leakage of albumin to the brain. However, considering the low protein concentration in cerebrospinal fluid of 2–3 g/L at most after a severe head injury, most likely reflecting approximately the same concentrations in the brain interstitium, these concentrations are very low compared to the normal plasma protein concentration of approximately 60 g/L. Protein leakage cannot therefore have any significant influence on the transcapillary oncotic absorbing force in the brain. The plasma oncotic effect may help to maintain ICP at an adequate level or to reduce a raised ICP. There are insufficient data to give support for the use of synthetic colloids to severe TBI patients.

63.1.1 Erythrocyte Transfusion

No studies have been performed to date that can be used for guidance in the treatment with erythrocyte transfusion in patients with severe TBI. One study from Canada (Hébert et al. 1999) could not show any beneficial effects of erythrocyte transfusion in a general intensive care material, but no TBI patients were included and leukocyte-depleted blood was not used. A more recent study, on the other hand, showed

that higher haemoglobin concentrations are associated with improved outcome after subarachnoid haemorrhage (Naidech et al. 2007), and another study showed improved oxygenation of red blood cell transfusion regardless of baseline haemoglobin concentration (Zygun et al. 2009). Due to the uncertainty regarding optimal haemoglobin concentration, very low haemoglobin concentrations down to 70 g/L (4.3 mmol/L) have been accepted in many neurointensive care units, while other units aim at a haemoglobin concentrations above 110 g/L, as also recommended in the Lund concept (see Chap. 58).

Low haemoglobin concentrations mean larger plasma volume to maintain normovolaemia. This means a greater need for plasma volume expanders to reach normovolaemia from a hypovolaemic state, which also means more transcapillary leakage of plasma and more tissue oedema according to the two-pore theory. It has also been shown in the dog that plasma leakage to the interstitium is higher with a low haemoglobin concentration than with a more normal one (Valeri et al. 1986). These considerations indicate that haemoglobin concentration is of importance in the fluid therapy of TBI patients, and a relatively normal haemoglobin level may be optimal. Normalisation of a low haemoglobin value also improves oxygenation of the injured brain (Smith et al. 2005; Dhar et al. 2009). This may be of special importance for outcome in TBI patients as the hypoxic penumbra zone is the critical area of a traumatised brain to be saved.

As transplantation from another human being, blood transfusion does have side effects. Especially, it has proinflammatory effects when using non-leukocyte-depleted blood and when using blood stored for longer periods of time. Side effects of erythrocyte transfusion can be reduced by using leukocyte-depleted blood and fresher blood products (Bilgin et al. 2011). It is still not verified, however, to what extent the blood volume expanding effect and oxygenation effect of blood transfusion in TBI patients override any potentially adverse effects.

63.1.2 How to Confirm the Status of the Volumetric State

A relatively normal protein and haemoglobin concentration may help to maintain an adequate intravascular volume. The use of Swan-Ganz catheters, PiCCO catheters and other advanced vascular monitoring devices is rarely indicated in the treatment of TBI patients. The arterial blood pressure response on a bolus dose of a plasma volume expander or erythrocytes, the arterial blood pressure response following leg tilting and the PPV index of the arterial curve may be tools by which to evaluate the volumetric state of the patient.

63.1.3 Guidance on Fluid Treatment With Crystalloids and Albumin

The use of crystalloids as the dominating plasma volume expander means that relatively large volumes must be infused to maintain normovolaemia, and there is often a need for vasopressors to keep an adequate cerebral perfusion pressure. Be aware of the fact that this fluid therapy means general tissue oedema, including the lung and the injured brain with a disrupted BBB and that there is a potential risk of hyperchloraemic acidosis when using large volumes of saline.

In spite of the SAFE-TBI study, there is still support for the use of albumin up to relatively normal albumin concentrations (33–37 g/L), if used adequately. Even though 20% albumin is to be preferred, also lower concentrations can be used. Avoid over-transfusion with albumin. In addition, a crystalloid solution should be used (e.g. 1–1.5 L/day for an adult) to maintain an adequate fluid balance and urine production.

The need for albumin as a plasma volume expander can be restricted by (1) giving albumin at a low infusion rate (e.g. 100 mL of 20% albumin over 4 h), (2) avoiding high arterial pressures by avoiding vasopressors and using antihypertensive treatment at supranormal blood pressures and (3) avoiding low haemoglobin concentration (>110 g/L) (leukocyte-depleted blood should be used).

63.1.4 Electrolytes

As with other patients in the intensive care setting, preservation of normal concentrations of electrolytes such as sodium, potassium and chloride ions is important in patients with a severe head injury. The infusion of potassium should be adapted to maintain its concentration within normal limits of 3.6–4.4 mmol/L. It is especially emphasised that low concentrations of sodium may have severe adverse effects in head-injured patients, as hyponatraemia can be associated with the development of brain oedema. Hypotonic solutions (both for albumin and crystalloid solutions) therefore must be avoided. If not adequately treated, hyponatraemia is quite common in these patients. Note the risk with adverse hyperchloraemic acidosis with large volumes of crystalloids resulting in high values of chloride ions. Treatment with osmotherapy in terms of hypertonic saline or mannitol may cause pronounced adverse hypernatremia. Hyponatremia, hypocalcaemia, hypophosphataemia, hypokalaemia and hypomagnesaemia may appear in head trauma patients, and these electrolytes should be determined regularly and if necessary be adequately supplemented.

Hyponatraemia after a head injury can be classified by the cerebral salt-wasting syndrome (CSWS) and the syndrome of inappropriate antidiuretic hormone secretion (SIADH). In CSWS, there is an elevation of brain natriuretic peptide (BNP) levels, which results in reduction in the efficacy of aldosterone and hence reduction in the ability to reabsorb sodium in the kidneys. This results in excretion of salt in the urine. The SIADH is more common in neurological patients and results from an excessive secretion of antidiuretic hormone; water is retained with risk of hypervolaemia and reduced plasma sodium and should be treated with sodium substitution in combination with diuretics. CSWS is a more rare cause of hyponatraemia, but it may be diagnosed as hyponatraemia in combination with excessive production of slightly hypertonic urine. It should be treated with sodium substitution in combination with fluid substitution in volumes related to the amount of urine production. If the polyuria is extensive, the patient may be treated with low doses of ADH analogue. Adrenal gland failure may occur early after a traumatic brain injury and can be diagnosed from analysis of pituitary and adrenal hormones. If it results in severe hypoglycaemia, hypotension and hyponatraemia, treatment with adrenocorticotropin hormones can be considered.

63.1.5 Vasopressors

Previously, all traditional guidelines recommended the use of vasopressors to maintain a CPP of above 70 mmHg, and both inotropic support and vasoconstrictors such as phenylephrine and noradrenaline were used. By the change in the recommendations of CPP from a minimal value of 70 mmHg down to 50–60 mmHg in the update of the US guidelines from 2007 (The Brain Trauma Foundation 2007) and to 60–70 mmHg in the latest update from 2016 (The Brain Trauma Foundation 2016), the need for vasopressors has been reduced, if these guidelines are followed.

The use of lowest possible dose of vasopressors is recommended with the Lund therapy. Still, CPP stays in the range of 60–70 mmHg in most patients using this guideline in spite of the use of antihypertensive therapy. Most likely this is due to a more strict treatment of hypovolaemia by albumin infusions towards a relatively normal albumin concentration in plasma and by giving erythrocyte transfusion at low haemoglobin concentrations. According to the principles behind the Lund therapy, the use of lowest possible dose of vasopressors may reduce the increase in ICP, reduces the need for plasma volume expanders and results in a less compromised microcirculation and better oxygenation of hypoxic areas of the brain and in the rest of the body (see Chap. 55).

Tips, Tricks and Pitfalls

If using a crystalloid (always isotonic solutions) as the main plasma volume expander, be aware of the following:

- Relatively large volumes are needed to maintain normovolaemia.
- Crystalloids are associated with general tissue oedema, including the injured brain.
- Saline is associated with hyperchloraemic acidosis.

If using albumin (always isotonic solutions) as plasma volume expander, the need of albumin and the risk of hypovolemia may be reduced by:

- Using high-concentration solutions.
- Using low infusion rates.
- Avoiding high blood pressures and vasopressors.
- Avoiding low haemoglobin concentrations.
- Frequent physiotherapy to activate the lymphatic recirculation system.

63.2 Background

As in other trauma patients, the TBI patient suffers from a general increase in microvascular permeability, resulting in an increase in transcapillary leakage of plasma fluid to the interstitium (Bentzer and Grände 2017). This leakage results in hypovolaemia if the transcapillary escape rate (TER) (normally 5–8% of total plasma volume per hour) is increased above the capacity of the lymphatic recirculation system (Haskell et al. 1997). If not adequately treated, most patients with severe TBI suffer from hypovolaemia, resulting in activation of the baroreceptor reflex with increased sympathetic discharge and catecholamine release. Avoidance of hypovolaemia is essential in patients with severe TBI for maintenance of perfusion and oxygenation of the injured brain, especially the most injured parts of the brain (Rise et al. 1998). This means that there is a need for transfusion with blood volume expanders to restore blood volume to a normovolaemic condition.

In principle, we lack generally accepted clinical studies that could be used for guidance on fluid treatment in these patients. Saline and albumin are the most common plasma volume expanders used in clinical practice today for TBI patients. The only randomised study regarding fluid therapy in severe TBI patients published so far (The SAFE Study Investigators 2007) showed better outcome with normal saline than with 4% hypotonic albumin, while other smaller studies have all indicated beneficial effects with albumin (Tomita et al. 1994; Dubois et al. 2006; Bernard et al. 2008; Rodling Wahlström et al. 2009; Jungner et al. 2010). A large recent study also showed that low serum albumin and prealbumin predict a significantly worse outcome of traumatic brain injury (Chen et al. 2014). The SAFE-TBI study has resulted in more frequent use of normal saline and other crystalloids and much less frequent use of albumin during the last few years in many neurointensive care units all over the world.

Traditional guidelines such as the American Guidelines or the European Brain Injury Consortium guidelines—in their original or updated versions for treatment of TBI—do not suggest any strategies for fluid management (Bullock et al. 1996; Maas et al. 1997; Stocchetti et al. 2001; The Brain Trauma Foundation 2007; 2016). Thus, no consensus about the type of fluid substitution, which volumes and infusion rates to use, or which concentration of albumin solution to use for an optimal fluid treatment, has been developed. We also lack studies and recommendations about the optimal haemoglobin concentration in patients with severe TBI, an issue of importance not only regarding oxygenation of the brain, but

also regarding maintaining of an adequate blood volume, as erythrocytes comprise a large proportion of the blood volume. This is of added importance at a time where restraints, due to the risk of transfusion with contaminated blood, give rise to strict local criteria for blood transfusion. The two main plasma volume-expanding alternatives used today, crystalloids and albumin, in combination with their most important physiological features have been described above.

The unexpected results from the SAFE-TBI study may indicate that normal saline is a better choice than 4% albumin as plasma volume expander in TBI patients. The SAFE-TBI study has been criticised, however, for several reasons (Drummond et al. 2011; Van Aken et al. 2012). It was a subgroup study of 350 patients selected from a much larger study with 7000 general intensive care patients not designed to identify how human albumin affects outcome in patients with TBI. The SAFE-TBI study has been criticised because of this and the fact that subgroup analyses are always doubtful from a statistical point of view, especially if the groups differ at baseline. This was also the case in the SAFE-TBI study regarding baseline ICP and number of older patients, both differences negative for the albumin group. More important, however, was that they used a hypotonic human albumin solution of 250 mosm/kg compared with normal plasma osmolarity of 290 mosm/kg. Hypotonic solutions are contraindicated in TBI patients due to the risk of brain oedema development. Van Aker and co-workers (Van Aken et al. 2012) even declared that the albumin compound was not the deleterious factor in the SAFE-TBI study, but that it just confirmed that hypotonic solutions are deleterious in TBI patients. Considering the critic raised and the unexpected results of the SAFE-TBI study, it is reasonable to conclude that this study alone cannot be used to question the use of albumin in severely injured TBI patients. It was also concluded in a recent review that evidence from trials, no matter how impressive, should be interpreted with caution when only one trial is available (Ioannidis 2005). This statement is applicable to the SAFE-TBI study.

The fact that norepinephrine was used in high doses in the SAFE-TBI study to reach a CPP of above 70 mmHg may have been negative for outcome in the albumin group. It has been documented both experimentally and in patients that norepinephrine induces a significant loss of plasma proteins to the interstitium (Dubniks et al. 2007; Nygren et al. 2010). Increased loss of plasma by norepinephrine can be explained according to the two-pore theory for transcapillary exchange by an increase in hydrostatic capillary pressure and convection (Rippe and Haraldsson 1994). Especially for the albumin group, this may have resulted in extracranial complications in terms of general tissue oedema and ARDS (Contant et al. 2001; Grände 2008) and hypovolaemia. Thus, even though the SAFE-TBI study has been the only randomised study to be published so far regarding fluid therapy in TBI patients and to formally fulfil the demand for a Level II study, after critical evaluation, the results cannot be used for a general recommendation of avoiding albumin and using only normal saline or other crystalloids as plasma volume expander.

With the lack of recommendations in conventional guidelines on how to treat patients with severe TBI regarding plasma volume substitution, this chapter has described the two main alternatives used in clinical practice today: (1) a fluid regime using mainly crystalloids as recommended by the SAFE-TBI study and (2) an alternative regimen based on physiological and pathophysiological principles for transcapillary fluid exchange using albumin as colloid combined with crystalloids. In principle, the latter regimen agrees with that suggested in the Lund concept for treatment of severe TBI patients (Grände 2006, 2017), which is described in another chapter of this book (Chap. 55). This regimen recommends 1–1.5 L of an isotonic crystalloid combined with albumin 20% up to 33 g/L and normovolaemia. Synthetic colloids such as HES solutions and gelatin have previously been given as plasma volume expanders in TBI patients in Europe, but no human trials have been published giving support on TBI patients. A recent study also showed in a general intensive care material that HES solutions may cause

renal insufficiency. Gelatin consists of small molecules and behaves more or less like a crystalloid. Synthetic fluids therefore should not be used in head-injured patients.

References

Bark BP, Grände PO. Infusion rate and plasma volume expansion of dextran and albumin in the septic guinea pig. Acta Anaesthesiol Scand. 2014;58:44–51. https://doi.org/10.1111/aas.12228.

Bentzer P, Grände PO. Isolated brain trauma in cats triggers rapid onset of hypovolemia. Neurocrit Care. 2017;26:450–6. https://doi.org/10.1007/s12028-016-0348-5.

Bernard F, Al-Tamimi YZ, Chatfield D, Lynch AG, Matta BF, Menon DK. Serum albumin level as a predictor of outcome in traumatic brain injury: potential for treatment. J Trauma. 2008;64(4):872–5.

Bilgin YM, van Watering LMG, Brand A. Clinical effects of leucoreduction of blood transfusions. Neth J Med. 2011;69:441–5.

Bullock R, Chesnut RM, Clifton G, Ghajar J, Marion DW, Narayan RK, Newell DW, Pitts LH, Rosner MJ, Wiberger JW. Guidelines for the management of severe head injury. Brain Trauma Foundation. Eur J Emerg Med. 1996;3(2):109–27.

Chen D, Bao L, Lu S, Xu F. Serum albumin and prealbumin predict the poor outcome of traumatic brain injury. PLoS One. 2014;9(3):1–7.

Contant CF, Valadka AB, Gopinath SP, Hannay HJ, Robertson CS. Adult respiratory distress syndrome: a complication of induced hypertension after severe head injury. J Neurosurg. 2001;95(4):560–8. https://doi.org/10.3171/jns.2001.95.4.0560.

Dhar R, Zazulia AR, Videen TO, Zipfel GJ, Derdeyn CP, Diringer MN. Red blood cell transfusion increases cerebral oxygen delivery in anemic patients with subarachnoid hemorrhage. Stroke. 2009;40(9):3039–44.

Drummond JC, Patel P, Lemkull B. Proscribing the use of albumin in the head-injured patient is not warranted. Anesth Analg. 2011;113:426–7. https://doi.org/10.1213/ANE.0b013e31821ed699.

Dubniks M, Persson J, Grände PO. Effect of blood pressure on plasma volume loss in the rat under increased permeability. Intensive Care Med. 2007;33(12):2192–8.

Dubois MJ, Orellana-Jimenez C, Melot C, De Backer D, Berre J, Leeman M, Brimioulle S, Appoloni O, Creteur J, Vincent JL. Albumin administration improves organ function in critically ill hypoalbuminemic patients: a prospective, randomized, controlled, pilot study. Crit Care Med. 2006;34:2536–40.

Grände PO. The "Lund Concept" for the treatment of severe head trauma – physiological principles and clinical application. Intensive Care Med. 2006;32(10):1475–84.

Grände PO. Time out for albumin or a valuable therapeutic component in severe head injury? Acta Anaesthesiol Scand. 2008;52(6):738–41.

Grände PO. Critical evaluation of the Lund concept for treatment of severe traumatic head injury, 25 years after its introduction. Front Neurol. 2017. https://doi.org/10.3389/fneur.2017.00315.

Haskell A, Nadel ER, Stachenfeld NS, Nagashima K, Mack GW. Transcapillary escape rate of albumin in humans during exercise-induced hypervolemia. J Appl Physiol. 1997;83(2):407–13.

Hébert PC, Wells G, Blajchman MA, Marshal J, Martin C, Pagliarello G, Tweeddale M, Schweitzer I, Yetisir E. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. N Engl J Med. 1999;340(6):409–17.

Ioannidis JP. Contradicted and initially stronger effects in highly cited clinical research. JAMA. 2005;294:218–28. https://doi.org/10.1001/jama.294.2.218.

Jungner M, Grände PO, Mattiasson G, Bentzer P. Effects on brain edema of crystalloid and albumin fluid resuscitation after brain trauma and hemorrhage in the rat. Anesthesiology. 2010;112(5):1194–203.

Maas AI, Dearden M, Teasdale GM, Braakman R, Chadon F, Iannotti F, Karimi A, Lapierre F, Stochetti N, Unterberg A. EBIC-guidelines for management of severe head injury in adults. European Brain Injury Consortium. Acta Neurochir. 1997;139(4):286–94.

Naidech AM, Jovanovic B, Wartenberg KE, Parra A, Ostapkovich N, Cinnolly ES, Mayer SA, Commichau C. Higher hemoglobin is associated with improved outcome after subarachnoid hemorrhage. Crit Care Med. 2007;35(10):2383–9.

Nygren A, Redfors B, Thorén A, Ricksten SE. Norepinephrine causes a pressure-dependent plasma volume decrease in clinical vasodilatory shock. Acta Anaesthesiol Scand. 2010;54(7):814–20.

Rippe B, Haraldsson B. Transport of macromolecules across microvascular walls: the two-pore theory. Physiol Rev. 1994;74(1):163–219.

Rise IR, Risöe C, Kirkeby O. Cerebrovascular effects of high intracranial pressure after moderate hemorrhage. J Neurosurg Anesthesiol. 1998;10(4):224–30.

Rodling Wahlström M, Olivecrona M, Nyström F, Koskinen LO, Naredi S. Fluid therapy and the use of albumin in the treatment of severe traumatic brain injury. Acta Anaesthesiol Scand. 2009;53(1):18–25.

Smith M, Stiefel MF, Magge S, Frangos S, Bloom S, Gracias V, Le Roux PD. Packed red blood cell transfusion increases local cerebral oxygenation. Crit Care Med. 2005;33(5):1104–8.

Stocchetti N, Penny KI, Dearden M, Braakman R, Cohadon F, Iannotti F, Lapierre F, Karimi A, Maas A, Murray GD, Ohman J, Persson L, Servadei F, Teasdale GM, Trojanowski T, Unterberg A, European

Brain Injury Consortium. Intensive care management of head-injured patients in Europe: a survey from the European brain injury consortium. Intensive Care Med. 2001;27(2):400–6.

The Brain Trauma Foundation. The American Association of Neurological Surgeons; Congress of Neurological Surgeons. Guidelines for the management of severe traumatic brain injury 3rd edition. J Neurotrauma. 2007;24(Suppl 1):S1–106.

The Brain Trauma Foundation. The American Association of Neurological Surgeons; Congress of Neurological Surgeons. Guidelines for management of severe traumatic brain injury 4th edition. J Neurosurg. 2016;354(6314):893–6.

The SAFE Study Investigators. Saline or albumin for fluid resuscitation in patients with traumatic brain injury. N Engl J Med. 2007;357:874–84.

Tomita H, Ito U, Tone O, Masaoka H, Tominaga B. High colloid oncotic therapy for contusional brain edema. Acta Neurochir Suppl (Wien). 1994;60:547–9.

Valeri CR, Donahue K, Feingold HM, Cassidy GP, Altschule MD. Increase in plasma volume after the transfusion of washed erythrocytes. Surg Gynecol Obstet. 1986;162(1):30–6.

Van Aken HK, Kampmeier TG, Ertmer C, Westphal M. Fluid resuscitation in patients with traumatic brain injury: what is a SAFE approach? Curr Opin Anaesthesiol. 2012;25:563–5. https://doi.org/10.1097/ACO.0b013e3283572274.

Zygun DA, Nortje J, Hutchinson PJ, Timofeev I, Menon DK, Gupta AK. The effect of red blood cell transfusion on cerebral oxygenation and metabolism after severe traumatic brain injury. Crit Care Med. 2009;37:1074–8.