Hypertonic saline solutions for treatment of intracranial hypertension
Sabine Himmelseher

Purpose of review
This review aims to provide an update on recent knowledge gained on hypertonic saline solutions for the treatment of intracranial hypertension. Explanatory approaches to the mechanisms underlying the edema-reducing effects of the solutions are outlined, practical aspects of use are presented, and trials that assessed their clinical utility are highlighted.

Recent findings
With an established trauma system, hypertonic saline added to conventional fluid resuscitation did not improve long-term outcome in multiple injury with hypotension and brain trauma. In intensive care, hypertonic saline reduced intracranial hypertension after subarachnoid haemorrhage, brain trauma, and a variety of other brain diseases, including cerebral edema in acute liver failure.

Summary
Hypertonic saline solutions have evolved as an alternative to mannitol or may be used in otherwise refractory intracranial hypertension to treat raised intracranial pressure. With high osmolar loads, the efficacy of the solution is enhanced, but no simple relationship between the saline concentration and the clinical effects of a solution is established. Caution is advised with high osmolar loads because they carry increased risks for potentially deleterious consequences of hypernatremia or may induce osmotic blood–brain barrier opening with possibly harmful extravasation of the hypertonic solution into the brain tissue.

Keywords
cerebral edema, critical care, hypertonic-hyperoncotic saline solution, hypertonic saline solution, intracranial hypertension, osmolar load

Introduction
Multiple insults to the brain including head trauma, stroke, subarachnoid haemorrhage, or intracranial surgery may be complicated by cerebral edema, brain swelling, and life-threatening intracranial hypertension. Although recent evidence has suggested no breakthrough for improved outcomes with physiologic interventions such as hypothermia within this scenario, osmotic therapy remains a mainstay, nonevidence-based approach to treat raised intracranial pressure (ICP) [1,2]. A repeated use of mannitol, however (the most frequently applied supportive intervention), may be especially associated with serious adverse effects, such as intravascular volume depletion, rebound ICP elevation, and renal failure [1,3]. As an alternative therapeutic avenue, hypertonic saline solutions have gained renewed interest and, recently, more common application in neurocritically ill patients [3–5,6,7,8,9]. After effective and apparently safe use in a few patients not responding to mannitol [10], their employment has even been supported with some enthusiasm.

In contrast, there is uncertainty about administration protocols, suitable degree of osmolar load, and safety issues of hypertonic saline solutions. Trial-based data to guide practice are lacking, and prospective, long-term outcome-orientated investigations on hypertonic saline and intracranial hypertension have not yet been published. Until recently, only small-sized studies mostly from retrospective collections, case series/cohort analyses, or paediatric trials [4,7,8] were available. Fundamental concerns with use of hypertonic saline in the management of brain insults, however, are the potentially deleterious consequences of brain dehydration produced by the osmotic shifts. Symptoms of hypernatremia...
and dehydration manifest more frequently in small children and the elderly, and include mental confusion, lethargy, delirium, seizures, coma, and death.

Although there are only a small number of comparative trials evaluating mannitol against hypertonic saline in the treatment of intracranial hypertension [8], it has become popular to view hypertonic saline as having at least some advantages over mannitol. This is mainly due to the theoretical advantage that sodium chloride (1.0 compared with 0.9 mannitol) has a higher osmotic reflection coefficient across an intact blood–brain barrier (BBB) [2,5]. Less sodium permeability may evoke a greater increase in serum osmolality. The creation of a higher transendothelial osmotic gradient in the vascular compartment may lead to more interstitial and intracellular brain and body water extraction into the intravascular space. Improved brain edema reduction, better ICP decrease and perfusion increase are considered mainly to then attenuate secondary brain injury progression. Whether this disparity translates into a clinically meaningful difference between mannitol and hypertonic saline is unknown, however, and only a few clinical trials have compared hypertonic saline with other conventional osmotic agents. In addition, interpretations were often inappropriate because comparisons were not made at an equimolar dose and/or equivolumetric quantity of the agents applied [1–5,7,8,9]. Combined or sequential use of mannitol and hypertonic saline has confounded many observations, and patient eligibility for use of hypertonic saline has frequently been biased [8,9].

Moreover, there has been a recent trend to employ hypertonic-hyperoncotic solutions (HHS) for treatment of intracranial hypertension in the ICU [8]. HHS have been advocated for prehospital small-volume resuscitation to improve haemodynamic stability in haemorrhagic shock and/or brain injury [11]. Their impact on injured brain tissue has not been well studied, however, and there may be adverse effects from adding an artificial colloid solution to hypertonic saline, such as exacerbating coagulation impairments with hydroxyethyl starch (HAES).

In view of the increased clinical use of hypertonic saline, and to assess their potential utility for treatment of intracranial hypertension, it seems timely to highlight the latest publications on hypertonic saline and raised ICP with a focus on clinical reports. More early work will not be repeated, and for additional details, I refer my readers to previous, comprehensive reviews [1,2,7,8].

The basics: using hypertonic saline solutions to treat intracranial hypertension

For an appropriate use of hypertonic saline solutions, acute and intensive-care providers need to be familiar with practical concerns, safety issues, mechanisms of action, and potential side effects of osmotherapy with sodium chloride.

**Definitions and measurements**

Hypovolemia and hypo-osmolality are considered to be detrimental after brain injury, and physiologic serum sodium and osmolality values are considered to be essential in fluid and electrolyte therapy (Table 1) [12,13]. Hypertonic saline refers to any saline solution with a concentration of sodium chloride greater than physiologic saline (0.9%), and it can be used as a continuous infusion or in bolus form to prevent and/or treat intracranial hypertension. Table 2 shows the various concentrations of hypertonic saline and their corresponding osmolalities (Table 2). In case of poor intracranial compliance and high risk for intracranial hypertension, osmotherapy with hypertonic saline aims to induce serum hyperosmolality with sodium levels of approximately 145–155 mEq/kg and osmolalities of approximately 300–320 mOsm/kg. In case of refractory ICP increases, most prospective trials applied hypertonic saline when the ICP exceeded 20 mmHg for more than 5 min [14,15,16]. Although there is no common definition and management plan for refractory intracranial hypertension, there is an outline presentation where measures of sedation, cerebrospinal fluid (CSF) drainage, hyperventilation, paralysis, mannitol, and others have failed to meaningfully decrease the ICP. Here, hypertonic saline may still have effective pressure-lowering impact. In these settings, however, the general applicability of the 320-mOsm threshold value, as proposed in the Brain Trauma Foundation (BTF) Guidelines [1–5,17], has been questioned for hypertonic saline. The evidence for harmful sequelae necessarily associated with this ceiling is small, and supported by a few data on high-dose, continuously infused mannitol [5,17]. To maximize benefits from hypertonic saline, clinical trials and experts have reported crossing this boundary in everyday care, without complaining about an increase in grave adverse effects such as acute renal failure [18]. During such therapy, laboratory values should be monitored every 3–6 h, and meticulous attention to provide an adequate hydration status is necessary.

<table>
<thead>
<tr>
<th>Osmolality and sodium values to be monitored with use of hypertonic saline solutions</th>
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<tr>
<th>Physiologic ranges</th>
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<tr>
<td>Serum osmolality</td>
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<td>Serum sodium</td>
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<th>Levels used in case of poor intracranial compliance/elastance – high risk for intracranial hypertension</th>
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<tr>
<td>Serum osmolality</td>
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<th>Possibly dangerous threshold values – exact boundaries debated and to be individualized according to patient circumstances</th>
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<tbody>
<tr>
<td>Serum osmolality</td>
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<td>Serum sodium</td>
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Osmolality values are to be taken with blood urea nitrogen and glucose values within physiologic ranges.
The 320-mOsm/kg limit has been questioned, and sodium values between 150 and 160 mEq/l may be applicable in the paediatric population, especially after TBI, immediate postinjury use of hypertonic saline worsened tissue damage and edema at 24 h postinsult, whereas normal saline–albumin treatment attenuated brain water content [22]. In contrast, when hypertonic saline was infused with a 6-h delay, no exacerbation of brain injury and edema occurred. In a similar rat TBI model, an immediate decrease in ICP and a reduction in injured brain tissue volume were observed when a combined 7.5% hypertonic saline-10% HAES (200/0.5) solution was used within 15 min of contusion [23]. In a different injury paradigm of middle cerebral artery (MCA) occlusion inducing large stroke in rats, the peak of BBB disruption occurred at 48 h postinjury [24]. This phenomenon was not affected by increasing serum osmolalities up to 335 mOsm/kg with 3% or 7.5% hypertonic saline infused from 6 h postinsult onward [24]. With respect to upper threshold values, it was observed that serum osmolalities of 350–385 mOsm/kg were accompanied by some reduction of brain edema in the ischemic and nonischemic hemisphere 96 h postinsult. In another study by the same group, healthy rats showed a decrease in bowel, lung, and brain water content at serum osmolalities greater than 350 mOsm/kg without suffering from increased mortality [25]. After focal cerebral ischemia in otherwise the same rat model, stroke-related lung water increases were attenuated by hypertonic saline, which strongly correlated with increased serum osmolality. Unfortunately, these rat experiments did not assess recovery. This would have been very important, because a reduction in brain volume lesions does not necessarily translate into better cerebral outcome. In the cerebral microcirculation, hypertonic saline may improve vaso-regulation [2,5,6*] via decreased blood viscosity, endothelial edema and capillary resistance, and via dehydration of erythrocytes. An improved rheological situation may thus add to better brain-tissue perfusion and oxygenation. The intravascular volume expansion caused by hypertonic saline may improve the haemodynamic situation by increasing mean arterial pressure (MAP) and cardiac output [2,5,6**]. Subsequently, raised cerebral perfusion pressures (CPP) may add to decreased intracranial hypertension. When L-arginine was added to 7.5% hypertonic saline in a rat model of TBI and haemorrhagic hypotension, hypertonic saline and hypertonic arginine saline solutions similarly improved MAP, ICP and cerebral blood flow [26]. After TBI with the fluid percussion method, arginine did not further enhance beneficial effects of hypertonic saline on the cerebral circulation. Another new mechanism of hypertonic saline has been revealed in a rat MCA occlusion model. When 7.5% hypertonic saline was started with a 6-h delay after stroke, attenuated brain water content coincided with

Table 2 Theoretical osmolalities of solutions employed to treat intracranial hypertension

<table>
<thead>
<tr>
<th>Solution</th>
<th>Osmolality (mOsm/kg)</th>
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<tbody>
<tr>
<td>0.9% Saline</td>
<td>308</td>
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<tr>
<td>3% Saline</td>
<td>1026</td>
</tr>
<tr>
<td>7.5% Saline</td>
<td>2587</td>
</tr>
<tr>
<td>20% Saline</td>
<td>6844</td>
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<tr>
<td>23.4% Saline</td>
<td>8008</td>
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<tr>
<td>30% Saline</td>
<td>10 287</td>
</tr>
<tr>
<td>7.5% Saline/6% dextran</td>
<td>2588</td>
</tr>
<tr>
<td>7.2% Saline/6% HAES (200/0.6)</td>
<td>2464</td>
</tr>
<tr>
<td>10% Mannitol</td>
<td>550</td>
</tr>
<tr>
<td>15% Mannitol</td>
<td>825</td>
</tr>
<tr>
<td>20% Mannitol</td>
<td>1100</td>
</tr>
<tr>
<td>25% Mannitol</td>
<td>1375</td>
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HAES, hydroxethyl starch.

required [6**]. Nevertheless, severe hyperosmolality contraindicates a continuation of hypertonic saline. Interestingly, a recent study in patients with traumatic brain injury (TBI) receiving hypertonic saline for intracranial hypertension showed that calculated serum osmolalities [formula used: 2 × Na⁺⁺ + blood urea nitrogen (BUN) + glucose] compared poorly with cryoscopic osmometry measurements [19]. Calculations consistently overestimated measured osmolalities, which led to the conclusion that direct measurements are indispensable when osmolality is checked with hypertonic saline therapy. To assess dangerous upper thresholds for serum sodium and osmolality with respect to outcome, a recent retrospective analysis of more than 600 neurologic ICU patients found that mortality increased with hypernatremia, but only severe hypernatremia was independently associated with increased mortality [20*]. Worsened outcome was not encountered until sodium values exceeded 160 mEq/l. This would correspond approximately to a serum osmolality of 335–345 mOsm/kg (BUN and glucose within physiologic ranges). Another recent chart review on hypertonic saline treatment in children with cerebral edema even reported that coma and mortality rates did not differ after induction of serum sodium concentrations of 150–160 compared with 160–170 mEq/l [21]. Hypertonic saline must not be used, however, in the perinatal period because of hazards of ruptures of cerebral veins and intracranial haemorrhage. Whether hypertonic saline does have benefits in the paediatric population, especially after TBI, is under current investigation. Taken together, there is still uncertainty about the optimal target range for serum osmolality and sodium values to be used for therapy of intracranial hypertension with hypertonic saline in adults (Table 1). The 320-mOsm/kg limit has been questioned, and sodium values between 150 and 160 mEq/l may be applicable in individual circumstances.

**Explanatory approaches for reduction of intracranial hypertension with hypertonic saline solutions**

There are many possible mechanisms that may account for the reduction of cerebral edema and intracranial hypertension with hypertonic saline [2,4,6**]. As mentioned, the osmotic effects of dehydrating brain tissue with hypertonic saline probably require a BBB that is functional at least to some degree. In a rat model of cortical contusion TBI, immediate postinjury use of hypertonic saline worsened tissue damage and edema at 24 h postinsult, whereas normal saline–albumin treatment attenuated brain water content [22]. In contrast, when hypertonic saline was infused with a 6-h delay, no exacerbation of brain injury and edema occurred. In a similar rat TBI model, an immediate decrease in ICP and a reduction in injured brain tissue volume were observed when a combined 7.5% hypertonic saline-10% HAES (200/0.5) solution was used within 15 min of contusion [23]. In a different injury paradigm of middle cerebral artery (MCA) occlusion inducing large stroke in rats, the peak of BBB disruption occurred at 48 h postinjury [24]. This phenomenon was not affected by increasing serum osmolalities up to 335 mOsm/kg with 3% or 7.5% hypertonic saline infused from 6 h postinsult onward [24]. With respect to upper threshold values, it was observed that serum osmolalities of 350–385 mOsm/kg were accompanied by some reduction of brain edema in the ischemic and nonischemic hemisphere 96 h postinsult. In another study by the same group, healthy rats showed a decrease in bowel, lung, and brain water content at serum osmolalities greater than 350 mOsm/kg without suffering from increased mortality [25]. After focal cerebral ischemia in otherwise the same rat model, stroke-related lung water increases were attenuated by hypertonic saline, which strongly correlated with increased serum osmolality. Unfortunately, these rat experiments did not assess recovery. This would have been very important, because a reduction in brain volume lesions does not necessarily translate into better cerebral outcome. In the cerebral microcirculation, hypertonic saline may improve vaso-regulation [2,5,6**] via decreased blood viscosity, endothelial edema and capillary resistance, and via dehydration of erythrocytes. An improved rheological situation may thus add to better brain-tissue perfusion and oxygenation. The intravascular volume expansion caused by hypertonic saline may improve the haemodynamic situation by increasing mean arterial pressure (MAP) and cardiac output [2,5,6**]. Subsequently, raised cerebral perfusion pressures (CPP) may add to decreased intracranial hypertension. When L-arginine was added to 7.5% hypertonic saline in a rat model of TBI and haemorrhagic hypotension, hypertonic saline and hypertonic arginine saline solutions similarly improved MAP, ICP and cerebral blood flow [26]. After TBI with the fluid percussion method, arginine did not further enhance beneficial effects of hypertonic saline on the cerebral circulation. Another new mechanism of hypertonic saline has been revealed in a rat MCA occlusion model. When 7.5% hypertonic saline was started with a 6-h delay after stroke, attenuated brain water content coincided with
reduced serum arginine-vasopressin (AVP) concentrations at 72 h posts insult [27**]. This phenomenon may well be relevant for edema formation, because AVP affects the water balance of brain glia cells via adjustment of water permeability and electrolyte channel function [28]. These recent animal studies are limited, however, by lack of long-term behavioural outcome assessment, partially insufficient measures of fluid status, and statistical confounders from very small experimental group numbers. The inflammatory response may also be dampened by hypertonic saline via reduction of white blood-cell activation, endothelium-mediated adhesion, and cell tissue invasion [2,5,6**]. In a recent study in human endothelial cells and in mice, similar anti-inflammatory effects were observed with HAES at physiologically relevant concentrations when hypoxia-induced increases in endothelial vascular leakage and acute inflammation were attenuated [29]. In an ex-vivo laboratory setting, however, HAES and dextran applied at high concentrations increased human leukocyte antigen expression on lymphocytes and monocytes [30]. In multiply injured patients with hypovolemia, a recent trial on prehospital small volume resuscitation with a combined solution of 7.5% hypertonic saline-6% dextran-70 (HSD) found that HSD resuscitation results in transient inhibition of inflammatory marker expression and partial restoration of the monocyte phenotype [31*]. In the setting of cardiopulmonary bypass in a piglet model, the use of a combined preparation of 7.2% hypertonic saline-10% HAES (200/0.5) during hypothermic bypass (28°C, 150 min) reduced organ water extravasation and maintained an unchanged ICP [32]. Neurologic recovery was not evaluated, however. More work will thus certainly be necessary to shed some light on the effects of hypertonic saline, HAES, and combined HHS on the immune and inflammatory response after brain insults, and their meaning in the treatment of intracranial hypertension. In addition, although only now beginning to be understood, the induction of a hypertonic environment with hypertonic saline will impact upon brain cells’ structural integrity, cytoskeletal dynamics, and the intracellular milieu [33]. To survive, cells have to avoid excessive volume changes in response to extracellular hypertonicity from volume shrinkage through water loss and potentially overshooting volume regulatory increase mechanisms. As protein functions are very vulnerable to dilution and concentration, the alteration of transmembrane potentials and cytosolic ion composition will affect natriferic transport and, thus, local cerebral pH, brain metabolism and other processes. Whether hypertonic saline will evoke a stress response that may accentuate brain injury [34], or whether there will ultimately be protective [35] or edema-reducing effects at the cellular level, will probably depend on the extent of hyperosmolarity reached in brain parenchyma, and the degree of injury induced by the previous insult. In summary, hypertonic saline, HAES, and HHS initiate a multitude of complex events when used to treat intracranial hypertension. Competing effects may occur at different brain areas and at the cerebral ‘micro-localization level’. In animal stroke, TBI, and cardiopulmonary bypass models, hypertonic saline effectively decreased the ICP. For prolonged duration of effect, a continuous infusion of hypertonic saline may be necessary. The timing of hypertonic saline administration appears to be decisive for reduction of intracranial hypertension with respect to BBB integrity, especially when hypertonic saline is used alone. As shown in a recent excellent study in a mouse TBI model, the period of potential secondary damage from BBB disruption and the time frame during which solutions have access to the injured brain may be longer than previously thought [36**]. Whether use of albumin, dextran, or HAES as a colloid together with hypertonic saline or use of HHS in case of BBB restriction do have value, remain to be clarified. The colloid may reduce the fluid escape into the injured brain, but the risk of brain-tissue extravasation with possible edema aggravation exists. In rats, it seems feasible to cross the 320-mOsm/kg ceiling without inducing acute serious side effects, but possibly increasing osmotic benefits.

**Adverse effects of hypertonic solutions**

Hypertonic saline administration may be associated with cerebral and systemic adverse effects, which are briefly summarized [2,5,6**,8]. As described, a pressing concern for use of hypertonic saline in patients with BBB disruption or barrier opening in case of excessive osmolar load is the notion that hypertonic saline may extravasate into the brain tissue, raise water content, and cause the opposite of the desired action, that is, an increase in intracranial hypertension and exacerbated brain damage. Other basic concerns with hypertonic saline are the potentially deleterious consequences of hypernatremia and brain dehydration related to the osmotic shifts. With rising hypernatremia, hypertonic saline may alter levels of vigilance, and cause mental confusion, lethargy, delirium, seizures, brain-bleeding complications, vascular congestion, thrombosis, haemorrhagic infarction, coma, and death. Within therapeutic ranges, the most grave possible complication with use of hypertonic saline is a too rapid correction of (chronic) hyponatremia, causing central pontine and extra-pontine myelinolysis (CPM) [37–39]. The syndrome is characterized by osmolar-induced pons demyelination, presenting with a decline in consciousness and motor deficits culminating in quadriplegia. Although CPM has not been reported after hypertonic saline, rapid serum sodium increases must especially be avoided in alcoholic and malnourished patients [38]. Hypertonic saline should not be used in hyponatremia. In susceptible patients, volume expansion with hypertonic
saline may cause pulmonary and peripheral edema, or congestive heart failure. As hypertonic saline may induce acute renal failure, maintenance of euvolemia is a pre-requisite for its use. When applied in large quantity, hypertonic saline may affect clotting times and platelet aggregation. Hyperchloremic metabolic acidosis and hypokalemia requiring correction may be encountered. After continuous infusion over longer periods, a too-rapid withdrawal with a swift decline in hypernatremia may end up in rebound brain edema from water uptake. A gradual tapering after longer time use is thus indispensable [6**].

**Special safety issues: hydroxyethyl starch and the injured brain**

As a result of improved small-volume resuscitation with HHS as fluid replacement therapy in haemorrhagic shock and TBI, HHS and also hypertonic saline and HAES have been used in the setting of TBI and for treatment of intracranial hypertension [11]. Arguments in favour of adding colloids to hypertonic saline are a longer duration of effect of volume expansion and increased haemodynamic stabilization with better nutritive organ blood flow and CPP [8,40]. The use of colloids has been discussed because of safety concerns, however, especially after brain insults [41]. First, all synthetic colloids may cause renal failure, pruritus, and allergic reactions. Since anaphylaxis occurs less often after HAES than after dextran, however, HAES has become a preferred agent [11]. Second, as in the animal, the addition of colloids to hypertonic saline with BBB restriction is considered to be a double-edged sword: the colloid may decrease fluid escape into the injured brain or, in contrast, a colloid macromolecule deposition within the cerebral interstitium may exacerbate brain edema because of its oncotic activity. More recent trials on use of HAES after brain insults show the following: in situations with an intact BBB, a small study in adult patients with spinal anaesthesia reported that subsequent to a 500-ml HAES (200/0.5) infusion, no penetration of HAES into the CSF was detectable over 24 h [42]. In a few patients with TBI or subarachnoid haemorrhage (SAH) and signs of BBB impairment on cranial computed tomographic (CCT) scans, the penetration of HAES (200/0.5, 500–1000 ml) into the CSF was also evaluated. While there were easily detectable plasma concentrations, HAES could not be discovered in the CSF [43]. Unfortunately, the CCT scans were done within 48 h before HAES was applied, and only CSF that flowed spontaneously into an external drainage over an 8-h period was analysed. It is thus unclear whether the BBB regained functional status until HAES was started, and it must be considered that spontaneous CSF drops may not be representative for CSF from all brain spaces. In addition, CSF that is free of HAES does not automatically indicate lack of interstitial penetration of the starch, because the composition of the blood–CSF barrier is different from that of the BBB.

Third, after brain injury, haemostatic disturbances and intracranial bleeding have been associated with exposure to hetastarch (450/0.7 or 670/0.75) or HAES of varying molecular weight and substitution [41]. Mainly because of accelerated elimination, a new HAES preparation, HAES 130/0.4, with a low molecular weight and degree of substitution has been approved, and two recent trials in patients with brain insults show the following. After nonsevere acute ischemic stroke, a 4-day volume therapy with 6% HAES 130/0.4 at a dose of 1500 ml over 24 h did not differ with respect to haemostaseology or other safety issues in comparison with a crystalloid fluid therapy [44]. In addition, after TBI, a large-dose 6% HAES 130/0.4 infusion therapy (repeated doses up to 70 ml/kg/day) was compared with a 6% HAES 200/0.5 approach (used at approved dose limit of 33 ml/kg/day and albumin as add-on colloid) [45]. After 31 patients had been managed with a CPP-orientated protocol, an interim analysis revealed no difference in mortality, renal function, use of blood products, or a 30% rate of intracranial bleeding complications between the two regimens. These bleeding events were interpreted as within frequencies reported in the literature and nonrelated to the study. Nevertheless, the trial was voluntarily terminated in view of an increased incidence of intracranial hypertension after HAES 200/0.5/albunin. The following intense debate focused on pro and contra arguments for coagulatory disturbances possibly caused by higher dose HAES in this setting, but interpretations ended in the area of speculation [46]. Interestingly, the role of albumin in relation to the ICP increases was regarded as unknown, and brain tissue deposition was not considered. Importantly, a recent retrospective analysis of 78 patients with severe TBI treated with crystalloids and 10% HAES (200/0.5) at 1000 ml/day did not report any bleeding complications in a CPP-directed protocol [47*]. In summary, major concerns on safety issues with use of HAES in brain injury have not yet been completely resolved, but adverse effects may be more pronounced when more than 1.51 HAES is used per day. Overall, it seems prudent to carefully check brain-diseased patients for neurologic deterioration with use of HAES. Whether fluid combinations of hypertonic saline and HAES as separate preparations or as a united solution may serve to contain complications of one or the other fluid substitute in the area of brain insults warrants further study.

**Trial-based knowledge: the clinical utility of hypertonic saline**

Although a few well executed prospective trials have provided new information on hypertonic saline, which is helpful to better assess its clinical utility, it should be considered that most studies were pilot observations or very small-numbered trials (Tables 3a and 3b).
### Table 3a Prospective trials on hypertonic saline and raised intracranial pressure published in the last 5 years

<table>
<thead>
<tr>
<th>Reference/ evidence</th>
<th>Study type</th>
<th>Size</th>
<th>Study solutions and setting</th>
<th>ICP before infusion</th>
<th>Primary study end point/ observation period</th>
<th>Secondary study end points</th>
<th>Outcome/specialties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bentsen et al. [63*]</td>
<td>Single-blinded randomized placebo-controlled trial</td>
<td>22 patients</td>
<td>7.2% hypertonic saline in 6% hydroxyethyl starch (200/0.5) compared with 0.9% saline placebo 2 ml/kg, as continuous infusion over 30 min ICU, after spontaneous subarachnoid haemorrhage</td>
<td>Stable ICP, 10–20 mmHg</td>
<td>Intracranial pressure/210 min Greater ICP-decrease after hypertonic saline Maximal mean CPP-increase: –6 mmHg, approx. 65 min after HS At study end, 210 min after HS: mostly, ICP still less than baseline</td>
<td>Greater increase in cerebral perfusion pressure after HS: Maximal mean CPP-increase of +6 mmHg at 60 min after HS Increase in cardiac index after HS-HAES No differences in extravascular lung water and intrathoracic blood volume indices</td>
<td>Outcome not reported Peak osmolalities measured after HS-HAES Approx. 332 mOsm/kg</td>
</tr>
<tr>
<td>Lescot et al. [56**]</td>
<td>Observational study</td>
<td>14 patients</td>
<td>20% hypertonic saline, 40 ml as continuous infusion over 20 min CT-suite, 1–5 days after traumatic brain injury</td>
<td>ICP &gt;20 mmHg for more than 15 min</td>
<td>CCT-changes, 2 min after HS: 2 min after cessation of HS Outcome not reported</td>
<td>HS exerts opposite effects on non-contused and contused areas 6 mmHg ICP-decrease CCT-changes not affected by: Contused tissue: increase in volume, no change in density Non-contused hemisphere: decrease in volume and increase in specific gravity with wide variability 2 min after cessation of HS: 6 mmHg ICP-decrease No change in heart rate, blood pressure, CPP, or end-tidal CO₂</td>
<td>Outcome not reported CTT-changes not affected by: age, initial GCS, mechanisms of accident, time delay trauma to CTT, ICP between responders and non-responders to HS</td>
</tr>
<tr>
<td>Huang et al. [16*]</td>
<td>Observational study</td>
<td>18 patients</td>
<td>3% hypertonic saline, 300 ml as continuous infusion over 20 min ICU, after traumatic brain injury</td>
<td>ICP &gt;20 mmHg</td>
<td>Intercranial pressure/60 min Greater CPP-increase at 30 min and at 60 min after HS-HAES than after mannitol</td>
<td>Maximal mean CPP-increase: +7 mmHg at 20 min and +9 mmHg at 60 min after HS No effect on blood pressure</td>
<td>Outcome not reported Transcranial Doppler measurements after HS: drop of pulsatility index, increase in flow velocity in middle cerebral artery HS: 10 survivors 7 deaths Mannitol: 6 survivors 9 deaths Haemodynamic values and serum osmolality increases not different after HS-HAES compared with mannitol</td>
</tr>
<tr>
<td>Harutjunyan et al. [15]</td>
<td>Randomized trial</td>
<td>32 patients</td>
<td>7.2% hypertonic saline in 6% hydroxyethyl starch (200/0.5) compared with 15% mannitol as continuous infusion until ICP &lt;15 mmHg ICU, after brain infarct, isolated head trauma, subarachnoid or intracerebral haemorrhage</td>
<td>ICP &gt;20 mmHg for more than 5 min</td>
<td>Intercranial pressure/60 min Greater CPP-increase at 30 min and at 60 min after HS-HAES than after mannitol</td>
<td>Greater CPP-increase at 30 min and at 60 min after HS-HAES than after mannitol</td>
<td>Outcome not reported</td>
</tr>
<tr>
<td>Battison et al. [14]</td>
<td>Randomized cross-over trial</td>
<td>9 patients</td>
<td>7.2% hypertonic saline in 6% dextran-70 (100 ml) compared with 20% mannitol (200 ml) as rapid infusion over 5 min ICU, after traumatic brain injury or subarachnoid haemorrhage</td>
<td>ICP &gt;20 mmHg for more than 5 min</td>
<td>Intercranial pressure/60 min Greater and longer-lasting decrease in ICP after HS-dextran than after mannitol</td>
<td>One difference, only: greater increase in minimum CPP after HS-dextran than after mannitol</td>
<td>Outcome not reported Comparison of equimolar doses (250 mOsm) of study solutions</td>
</tr>
</tbody>
</table>

CCT, cranial computer tomography; CPP, cerebral perfusion pressure; GCS, Glasgow Coma Score; HS, hypertonic saline; HS-HAES, 7.2% hypertonic saline/6% hydroxyethyl starch (200/0.5); ICP, intracranial pressure; ICU, intensive care unit; IV, intravenous.
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<thead>
<tr>
<th>Reference/ evidence</th>
<th>Study type</th>
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<tr>
<td>Cooper et al. [49]</td>
<td>Double blinded randomized placebo controlled multicentre trial</td>
<td>226 patients</td>
<td>7.5% hypertonic saline compared with 0.9% saline placebo 250ml each as rapid infusion Prehospital resuscitation for hypotension after brain trauma or brain and multisystem injury</td>
<td>Prehospital ICP not known</td>
<td>6-months neurological outcome: no difference in Glasgow Outcome Score, in favourable outcomes, or in any other post-injury measure of neurological function</td>
<td>6-months survival: no difference in survival rates</td>
<td>Large controlled prehospital multicentre trial Both groups received almost identical amounts of prehospital resuscitation fluids in addition to the study solution</td>
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<tr>
<td>Bentsen et al. [62]</td>
<td>Observational study</td>
<td>7 patients</td>
<td>7.2% hypertonic saline in 6% hydroxyethyl starch (200/0.5) (2 ml/kg) as continuous infusion over 20 min ICU, after spontaneous subarachnoid haemorrhage</td>
<td>ICP ≥20 mmHg or CPP &lt;60 mmHg for more than 5 min</td>
<td>Intracranial pressure/210 min 58% maximum ICP-decrease at 40 min after start of infusion 26% maximum CPP-increase at 40 min after start of infusion</td>
<td>4 of the 7 patients survived to hospital discharge</td>
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<td>Murphy et al. [61]</td>
<td>Randomized placebo controlled trial</td>
<td>30 patients</td>
<td>30% hypertonic saline infused at a rate of 6–20 ml/h to maintain serum sodium levels at 145–155 mmol/l Applied in addition to standard care vs. standard care ICU, after spontaneous subarachnoid haemorrhage</td>
<td>Initial ICP (mean) of all patients before admission to study: Approx. 17 mmHg</td>
<td>Intracranial hypertension (episodes of ICP &gt;25 mm Hg for &gt;10 min)/3 days 7 standard- and 3 HS-patients reached an ICP &gt;25 mm Hg Cumulative risk for intracranial hypertension greater without HS during the 3-day-period: Over the 1st day with standard: higher relative increase in norepinephrine needs Over the 1st day with HS: Relative decrease in ICP At 42 h: less ICP with HS than with standard</td>
<td>During the 7-day-period: no differences in episodes of CPP &lt;70 mmHg or other haemodynamic parameters No difference in high number of in-hospital patient deaths between the two groups</td>
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<tr>
<td>Vialet et al. [55]</td>
<td>Randomized trial</td>
<td>20 patients</td>
<td>7.5% hypertonic saline vs. 20% mannitol 2 ml/kg, as continuous infusion over 20 min ICU, after traumatic brain injury</td>
<td>ICP &gt;25 mmHg for more than 5 min</td>
<td>Intracranial hypertension/7 days fewer episodes and less duration of intracranial hypertension after HS</td>
<td>After 90 days: no difference in mortality and neurologic outcome between groups With HS: fewer treatment failures (no reduction of ICP &lt;35 mmHg or increase of CPP &gt;70 mmHg)</td>
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CPP, cerebral perfusion pressure; HS, hypertonic saline; ICP, intracranial pressure; ICU, intensive care unit.
Prehospital hypertonic saline in multisystem injury, hypotension and severe brain trauma: a multicentre outcome trial

A decrease in mortality and an increase in recovery can be achieved by reducing hypoxia and hypotension in the field through implementation of the BTF guidelines for the prehospital management of TBI [48]. In a large multicentre, double-blind, controlled trial, 226 patients with multiple injuries, TBI, and hypotension randomly received either 250 ml 7.5% hypertonic saline or 250 ml Ringer’s lactate solution in addition to fluid resuscitation with crystalloids and colloids (Table 3b) [49]. When 6-month outcomes were analysed, no intergroup differences in survival rates, favourable or good neurologic outcome, or any other postinjury measure of neurologic function could be detected. Unexpectedly, an almost identical volume of fluid replacement (1250 ml) had been administered in the field in both groups apart from the study solution. Hypotension upon hospital arrival had nevertheless to be corrected in both parties. In the ICU, first ICP measurements revealed a trend for a lower ICP after hypertonic saline. When deciphering these results from the prehospital arena, it must be taken into account that conditions in the field are uncontrolled, but it should be stressed also that the study protocol did not standardize treatment in the ICU or any other later therapy. Choice of fluid for trauma resuscitation is an area of controversy [50], but the mixed fluid strategy applied cannot easily be interpreted. Hypertonic saline appeared to be devoid of beneficial long-term effects, but it remains unclear whether the lack of improvement was due to lack of efficacy of hypertonic saline or a dilutional effect induced by rapid infusion of the other fluids used together with hypertonic saline. Questions about the value of a combination preparation of hypertonic saline and HAES and the potential improvement to be achieved with HHS have definitely not been resolved with this study. In summary, the trial showed that with the infrastructure of an established trauma system and well trained paramedics, 250 ml 7.5% hypertonic saline added to a fluid resuscitation strategy in the field did not improve long-term (neurologic) outcome from multiple injury with posttraumatic hypotension and severe blunt head injury.

Hypertonic saline and intracranial hypertension after subarachnoid haemorrhage or severe traumatic brain injury in intensive care

The triad of vasomotor paralysis with substantial reduction in cerebral blood flow [51], cerebral edema with elevated ICP [52], and increased cerebral blood volume is considered to critically contribute to poor brain perfusion, cerebral ischemia, infarction, and eventually poor outcome after SAH. In an initial case series in poor-grade patients with SAH, 23.5% hypertonic saline (2 ml/kg, infused over 20 min) served to provide a decrease in ICP (effect-half life: 2 h) and in cerebrovascular resistance (effect-half life: 20 min), and caused a 20–50% increase in cerebral blood flow in ischemic brain as examined with xenon-computed tomography [53]. These effects were accompanied by improved rheology indexes. Upon treatment with this highly concentrated hypertonic saline, serum sodium levels increased by approximately 11 mEq/l and osmolality rose by 27 mOsm/kg within the first hour. The half-life of serum sodium with one therapeutic episode was 12 h. No other serious adverse effects were reported. As intracranial steal phenomena were detectable in one region of interest only, further elucidation of hypertonic saline in severe SAH was decided. The currently ongoing follow-up evaluation confirmed that in (so far) 14 reported poor-grade SAH patients, 23.5% hypertonic saline may cause a decrease in ICP, an increase in MCA blood flow velocity and, in most cases, an increase in regional cerebral blood flow [54]. In addition, brain-tissue oxygen pressures increased with a peak at about 30 min postinfusion, and there was a tendency for an improved lactate–pyruvate ratio. No serious adverse events occurred, although the repeating of a treatment episode was subjected to restriction from hypernatremia. In conclusion, within the limits of these first patient observations, 23.4% hypertonic saline augmented regional cerebral blood flow after poor-grade SAH, reliably decreased raised ICP, and may act beneficially on brain metabolism. Further stroke-related and outcome-related trials and perhaps a pilot study on hypertonic saline in cerebral vasospasms after SAH with larger patient numbers are worth consideration.

In the early phase of TBI, the therapeutic goal for use of hypertonic saline is to reduce an acute and/or refractory ICP increase, and later, to prevent low serum sodium levels and thus cerebral edema. The practical aspects of hypertonic saline administration to patients with TBI have recently been published in a crisp neuroscience care-orientated compilation [6**], and the experience an academic centre has made with implementing hypertonic saline as a treatment for intracranial hypertension has lately been presented [12]. In recent prospective trials, the efficacy of hypertonic saline in decreasing intracranial hypertension was reported (Table 3a and 3b). When iso-volumetric (2 ml/kg) 7.5% hypertonic saline was compared with 20% mannitol in 20 severely head-injured patients in a randomized trial over about a 1-week period, hypertonic saline reduced the number of episodes and duration of intracranial hypertension approximately two times more effectively than mannitol [55]. A comparison of the osmotic load revealed that hypertonic saline delivered approximately 361 mOsm and mannitol 175 mOsm. Within 4 h of therapy, this caused a rise in serum osmolality up to 314 mOsm/kg after hypertonic saline and to
296 mOsm/kg after mannitol. No serious adverse effects were reported, but the analysis of the 90-day outcome data showed no difference in mortality or poor outcomes between the groups. Altogether, this trial confirms that an increased osmolar sodium load as delivered by hypertonic saline in comparison with less concentrated mannitol may more effectively treat intracranial hypertension after severe TBI. Unfortunately, however, the benefits of hypertonic saline did not translate into a better patient outcome. The immediate efficacy of 3% hypertonic saline (200 ml, over 20 min) in treating a raised ICP was also reported in a recent observational study in 18 patients with severe TBI [16]. The ICP decrease persisted over 1 h and was accompanied by an increase in CPP. No adverse effects were observed when 3% hypertonic saline was applied once in 24 h only. Any severe complication from hypernatremia should thus be prevented. As the osmolality of 3% hypertonic saline is comparable with that of 20% mannitol (Table 2), the results of this study add to the view that hypertonic saline may be used as an effective and safe alternative to mannitol when applied at similar osmolality.

A recent landmark investigation in 14 patients performed at 1–5 days after severe TBI demonstrated, however, that 20% hypertonic saline (40 ml) infused over 20 min exerted opposite effects on contusioned and noncontusioned brain areas [56**]. Based on quantitative assessments of CCT scans with dedicated imaging analysis [57,58], the trial showed that hypertonic saline decreased the volume of the noncontused hemisphere with a concomitant increase in specific gravity, whereas hypertonic saline increased the volume of the contused hemisphere without a change in density. These effects occurred at serum sodium levels of 146 ± 5 mEq/l. Overall, the ICP decreased from 23 ± 3 to 17 ± 5 mmHg. In addition, there was a wide variability in the change of specific gravity of the noncontused hemisphere in response to hypertonic saline. These excellent patient data allow for several important interpretations. First, the wide variability of the response of noncontused areas implies that the BBB integrity is unequally affected among patients after TBI. Second, because the response to hypertonic saline did not depend on patient age, initial Glasgow Coma Score, accident mechanism, delay between trauma and CCT, or ICP between responders and nonresponders, the status of BBB impairment may not easily be judged in the clinical setting. Slight, but perhaps critical, changes in BBB permeability may correctly be assessed with small molecules such as salt only. Third, in contused brain regions, the persistence of BBB disruption obviously occurred over a period of days. Of course, one could argue that applying 20% hypertonic saline is a too highly concentrated saline version in severe TBI, and should not be used in this setting, but 23.4% hypertonic saline has recently been praised for allegedly beneficial or at least preferential ICP-reducing effects in a chart review on its use in brain-injured patients not responding to mannitol [9]. As a whole, although the exact clinical relevance of the reported phenomenon for the brain is not really known, the data also show that with use of hypertonic saline, a BBB restriction in patients may be worsened, and that this may occur at later time periods after the initial trauma than thought before. Whether this could have further consequences for the injured and noninjured brain in the sense of extravasation of fluids, drugs, and other therapeutic or diagnostic agents used as solutes in neurocritical care, remains to be clarified. Far beyond, in a worst case imaginable scenario, highly concentrated hypertonic saline may exert additionally damaging effects on contused or even noncontused brain tissue even if employed several days after the initial insult.

In conclusion, hypertonic saline appears to effectively decrease episodes of intracranial hypertension after TBI; its exact duration of ICP-lowering effects and its efficacy of ICP-reduction are difficult to predict in general. Most studies assessed the ICP over a 1–2 h interval after hypertonic saline administration, during which the ICP remained decreased in most cases. When used in nonresponders to mannitol or under conditions of ICP extremes, highly concentrated hypertonic saline may still reduce intracranial hypertension. The risks for serious unwanted effects increase with rising saline concentrations, however, and the hazards for injured and noninjured brain tissue may become exacerbated. Overall, outcome data on long-term sequelae of hypertonic saline treatment on the brain are lacking.

Hypertonic saline and intracranial hypertension in fulminant liver failure

Refractory intracranial hypertension is a devastating complication of fulminant, acute hepatic failure, which is associated with high morbidity and mortality [59,60*]. The underlying pathophysiology is not understood, but the complex interfering processes likely originate from the lack of hepatic (ammonium) detoxification. Cerebral edema and brain swelling probably arise from accumulation of glutamine and water within astrocytes, and cerebrovasodilation and increased cerebral blood volume may be brought about by an inflammatory response syndrome and toxic products of the diseased liver [59,60*]. Only liver transplantation definitely improves outcome, but cerebral herniation prior to the availability of a donor organ often causes death [60*]. In this setting, hypertonic saline has been regarded as a promising therapeutic approach to treat intracranial hypertension. Moreover, hyponatremia is common with acute hepatic failure, and may add to the development of cerebral edema. As an example for a contemporary study on hypertonic saline as a therapy of
intracranial hypertension in acute hepatic failure, a prospective trial on 30 patients reported the following. After randomization to standard ICU therapy or standard ICU therapy and hypertonic saline, an infusion of 30% hypertonic saline to maintain serum sodium levels at 145–155 mEq/l [61] was employed (Table 3b). Upon delivery of a very high osmolar load in the first 24 h of therapy, that is ~780 mOsm on average, the ICP decreased relative to its value at the beginning of the infusion. Overall, the incidence of intracranial hypertension (ICP ≥ 25 mmHg) was less with hypertonic saline as compared with standard therapy in the 72-h observation. Although almost all patients received haemofiltration, however, many did not reach the end of the 72-h time period because of death or transplantation. Patient characteristics, hyponatremia, complications, transplantations, or mortality rates were not different between groups. Taken together, this study indicates that highly concentrated hypertonic saline may decrease intracranial hypertension in acute hepatic failure. The amount of osmolar load required may be rather extreme, however, and the risks of inducing harmful hyponatremia or additional brain damage may become exacerbated. Even in desperate situations with respect to ICP rises, very high osmolar loads should therefore not be applied without the availability of haemofiltration to buffer serum sodium levels. Whether treatment of intracranial hypertension with hypertonic saline in acute hepatic failure definitely serves as a bridge to buy time through ICP-lowering effects remains to be studied further.

**Hypertonic-hyperoncotic saline colloid solutions and intracranial hypertension in neurocritical care diseases and brain insults**

The rationale for employing HHS in the ICU setting is the therapeutic goal of simultaneously combining beneficial effects of hypertonic saline and HAES to prolong haemodynamic improvement and ICP-lowering action [11]. Although there has been a trend of using HHS to treat intracranial hypertension in the ICU after various brain insults [8], little is known about the interaction of the two components with respect to their impact on healthy and injured human brain.

Lately, the utility of a pharmacological combination preparation of hypertonic saline and HAES (hypertonic saline-HAES) has been subjected to first evaluations in neurocritically ill patients with intracranial hypertension. Hypertonic saline-HAES is composed of 7.2% hypertonic saline/6% HAES 200/0.5. In a small first pilot observation in seven severely diseased SAH patients, hypertonic saline-HAES (2 ml/kg, infused over 20 min) reliably decreased the ICP for a 3-h time period without causing adverse effects [62]. In another recent prospective trial in 22 patients with SAH, the effects of hypertonic saline-HAES on ICP and CPP were compared with those of isovolumetric normal saline placebo over a 210-min observation period [63] (Table 3a). This study must be regarded as an excellent hypothesis-driven trial because the design was laid out to detect quantifiable effects of hypertonic saline-HAES on the ICP in a direct comparison with placebo. Nevertheless, there are two strongly differing points of view. As medical obligations require treatment of an ICP greater than 20 mmHg with a verum drug, the investigations had to be performed in patients with a stable ICP of 10–20 mmHg to allow for a placebo group. In my opinion, such conditions may not be representative for patients with intracranial hypertension and an increased ICP greater than 20 mmHg. In the study, hypertonic saline-HAES (2 ml/kg infused over 30 min) reliably decreased the ICP with a maximum (~6 mmHg) effect occurring at twice the time of the infusion duration. This ICP reduction was greater than that after the placebo. Hypertonic saline-HAES also increased the CPP and the cardiac index, whereas intrathoracic blood volume and extravascular lung water indexes were not different between the groups. At the end of the study of drug infusion, the maximum serum sodium increase was +6 mmol/l, and the highest osmolality measured 332 mOsm/kg. No adverse effects were observed, although the 320-mOsm threshold was crossed. Outcome data were not reported. In summary, all of the observations reported in this trial may well be related to the hypertonic saline-HAES solution studied. In the previous pilot trial in patients with SAH and increased ICP greater than 20 mmHg, a smaller treatment effect occurred with the same hypertonic saline-HAES preparation [62]. This may be attributable to the reduction of the intracranial compliance that was present in that setting. Overall, these two first studies on hypertonic saline-HAES in patients with SAH show that hypertonic saline-HAES may be used to reliably decrease a raised ICP without inducing obvious, serious adverse effects. Nevertheless, it would be interesting to know whether a smaller volume or concentration of hypertonic saline-HAES would produce similar ICP-reducing effects with respect to magnitude and duration of action. Further work should be directed to identify better tailored choices of volumes and concentrations of HHS necessary to reduce intracranial hypertension, and an evaluation of these refined regimens on long-term outcome after SAH may be worth while.

In a different, more recent, crossover trial in nine patients with TBI suffering from an ICP greater than 20 mmHg, rapid equimolar infusions of 20% mannitol were compared with 7.5% hypertonic saline-6% dextran to treat intracranial hypertension [14] (Table 3a). Although small with respect to patient numbers, this important study directly compared the effects of an equimolar dose (approximately 250 mOsm) of mannitol with HSD. Both study solutions effectively decreased the ICP, but HSD
caused a greater reduction and a longer duration of effect than mannitol. No relevant changes occurred in the other important physiologic variables noted, and there were no serious adverse events. The interpretation of these data is clear: the clinical trial confirms much of the animal work described with respect to beneficial effects of combining HHS to treat raised ICP. The study explicitly noted that all patients were managed with a CPP-orientated protocol by a bedscape nurse meticulously adhering to the guidelines. HSD does therefore have clear advantages over mannitol in reducing intracranial hypertension when the general volume status is balanced.

Another more recent study in neurocritically ill patients with TBI, SAH, brain infarcts, and other cerebral insults with intracranial hypertension of more than 20 mmHg examined the dose of hypertonic saline-HAES necessary to cause an ICP decrease to a level below 15 mm Hg [15]. After randomization, 17 patients received hypertonic saline-HAES and 15 were treated with 15% mannitol. With a mean effective infusion dose of 1.4 ml/kg for hypertonic saline-HAES and 1.8 ml/kg for mannitol, both hypertonic solutions achieved an ICP decrease to the requested threshold of below 15 mmHg. During the 60-min observation period, hypertonic saline-HAES induced a greater decrease in ICP than mannitol. Both study solutions increased the CPP within their respective treatment group. No relevant effects on other important parameters were reported, and there was no difference in the number of survivors between the groups. Overall, those who survived required lower doses of osmotic agents. The results of this study are not surprising because 15% mannitol does transport a much lower osmolar load than hypertonic saline-HAES (Table 2) when infused with approximately the same volume. The more effective ICP reduction with hypertonic saline-HAES may thus be explained by this osmolar difference. It is, however, unclear why hypertonic saline-HAES was associated with a rather small increase in serum sodium levels and osmolarity.

In summary, in the more recent, albeit very small trials, HHS provided an effective reduction of intracranial hypertension, and may be associated with improved ICP-reducing efficacy as compared with mannitol. Based on the few available observations, general statements about safety and efficacy can, however, not yet be made. Future studies should aim to evaluate answers to some of the basic questions about the effects of hypertonic saline or HHS on the injured and noninjured brain tissue, in addition to refining treatment schedules for a raised ICP. For example, the effects of hypertonic saline and HHS on cerebral perfusion and brain tissue metabolism should be studied. Last but not least, comparisons between different hyperosmolar solutions should really be performed at equimolar concentrations and equivolumetric doses under controlled conditions.

### Conclusion

In view of the small trial-based knowledge on use of hypertonic saline for treatment of intracranial hypertension, many questions for evidence-based strategies remain. Nevertheless, the recent literature suggests that hypertonic saline is evolving as a real alternative to mannitol or may be used in otherwise refractory intracranial hypertension. The exact duration of ICP-lowering effects and the efficacy of ICP reduction are difficult to predict in general, and will depend on individual patient circumstances. Safety data on hypertonic saline in the treatment of intracranial hypertension are very limited, however. With rising osmolar loads, the efficacy of the solution is enhanced, but no simple relationship between the saline concentration and the ICP-reducing effect is established. Nevertheless, caution is advised with high osmolar loads; they carry increased risks for potentially deleterious consequences of hypernatremia or may induce osmotic BBB opening with unfavourable, possibly harmful sequelae, such as hypertonic saline extravasation into the brain tissue. Future work should be directed to identify better choices for more tailored regimen with respect to volumes and concentrations of hypertonic saline or HHS to be applied in the various settings of brain insults associated with intracranial hypertension.

### References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:
- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 490).

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meability and electrolyte channel function, this phenomenon may well be arginine-vasopressin concentrations after 72 h. As the hormone arginine-vaso-
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39 Martin RJ. Central pontine and extra-pontine myelination: the osmotic de-


46 Woesemr R, Grauer MT, Dieterich HJ, et al. Influence of a long-term, high-dose volume therapy with 6% hydroxyethyl starch 130/0.4 or crystal-


50 Retrospective analysis of 78 patients with severe traumatic brain injury who were managed with crystalloids and 10% HAES (200/0.5) in a cerebral perfusion pressure-orientated protocol that did not reveal any bleeding complica-


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55 Viale R, Albanese J, Thomachot L, et al. Isovolume hypertonic solutes (sodium chloride or mannitol) in the treatment of refractory posttraumatic intracranial hypertension: 2 mL/kg 7.5% saline is more effective than 2 mL/kg 20% mannitol. Crit Care Med 2003; 31:1683–1687.


This is a landmark study performed in 14 patients with severe brain trauma at 1–5 days postinjury: 20% HS (40 ml) infused over 20 min was shown to exert opposite effects on contusioned and noncontusioned brain. Quantitative CCT scan analysis demonstrated that hypertonic saline decreased the volume of the noncontused hemisphere with a concomitant increase in specific gravity, whereas HS also increased the volume of the contused hemisphere without a concomitant change in density. In a worst case imaginable scenario, highly concentrated HS may therefore have damaging effects on injured or far beyond noninjured brain tissue even if infused at several days after brain trauma.


Intracranial hypertension in acute hepatic failure carries an extraordinarily high mortality rate and remains a challenging disorder for the critical care provider. The review describes our current understanding of the underlying pathophysiology and enumerates therapeutic approaches to treat intracranial hypertension including use of hypertonic saline.


63 Bentzen G, Breivik H, Lundar T, Stubhaug A. Hypertonic saline (7.2%) in 6% hydroxyethyl starch reduces intracranial pressure and improves hemodynamics in a placebo-controlled study involving stable patients with subarachnoid hemorrhage. Crit Care Med 2006; 34:2912–2917. This hypothesis-driven trial was designed to detect quantifiable effects of a combination preparation of hypertonic saline–hydroxyethyl starch on the intracranial pressure after subarachnoid haemorrhage in a direct comparison with placebo. To allow for a placebo group, however, only patients with a stable intracranial pressure of 10–20 mm Hg were included. Hypertonic saline–hydroxyethyl starch reliably decreased the intracranial pressure with a maximum effect occurring at two times the infusion period. No serious adverse effects were reported, although the 320-mOsm threshold was crossed.