neurocritical care society Neurocrit Care (2012) 17:117–130
DOI 10.1007/s12028-011-9649-x

REVIEW

Hyperosmolar Therapy for Intracranial Hypertension

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Published online: 17 November 2011

Abstract The use of hyperosmolar agents for intracranial hypertension was introduced in the early 20th century and remains a mainstay of therapy for patients with cerebral edema. Both animal and human studies have demonstrated the efficacy of two hyperosmolar agents, mannitol and hypertonic saline, in reducing intracranial pressure via volume redistribution, plasma expansion, rheologic modifications, and anti-inflammatory effects. However, because of physician and institutional variation in therapeutic practices, lack of standardized protocols for initiation and administration of therapy, patient heterogeneity, and a paucity of randomized controlled trials have yielded little Class I evidence on which clinical decisions can be based, most current evidence regarding the use of hyperosmolar therapy is derived from retrospective analyses (Class III) and case series (Class IV). In this review, we summarize the available evidence regarding the use of hyperosmolar therapy with mannitol or hypertonic saline for the medical management of intracranial hypertension and present a comprehensive discussion of the evidence associated with various theoretical and practical concerns related to initiation, dosage, and monitoring of therapy.

Keywords Hypertonic saline · Mannitol · Traumatic brain injury · Hyperosmolar agents · Intracranial pressure

Introduction

Hyperosmolar agents for intracranial hypertension are the mainstay of medical therapy for patients with cerebral edema. Current evidence suggests that both mannitol and hypertonic saline (HTS) are effective agents for managing acute intracranial hypertension in the setting of traumatic brain injury (TBI), intracranial hemorrhage (ICH), tumor, and stroke, yet Class I evidence for this therapy is sparse and most evidence is derived from either retrospective analyses (Class III) or from case series (Class IV). Several factors contribute to the difficulty in gathering Class I evidence for hyperosmolar therapy, including the heterogeneity of etiologies of elevated intracranial pressure (ICP), variability among the treatment algorithms applied by institutions and clinicians, and the logistical difficulties associated with studying this critically ill patient population and adjusting for their comorbidities.

The same challenges that limit the availability of Class I evidence for hyperosmolar therapy have also led to a confusing array of conflicting reports regarding criteria and strategies for initiation, dosage, and monitoring of therapy. In addition, a variety of theoretical and practical concerns regarding the safety profile and potential complications of

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hyperosmolar therapy persist, even among clinicians who regularly use these agents in their daily practice. While some of these questions and concerns are well-founded, others are not based on strong evidence yet have been handed down between generations of clinicians as practical knowledge. This practice results in dogmatic application of treatment strategies that are not evidence-based and can result in suboptimal patient care. Indeed, there are few therapies where fact, uncertainty, and myth coexist so closely as with hyperosmolar therapy.

The objective of this review is to examine carefully and comprehensively the body of clinical evidence regarding the use of hyperosmolar therapy with mannitol or HTS for the medical management of intracranial hypertension. For each agent, we present an evidence-based discussion of the mechanism of action, the indications for initiation of therapy, and the strategies for dosage and monitoring of therapy. We then present a careful analysis of the potential risks and adverse events associated with therapy—real, hypothetical, or perceived—and summarize the evidence available regarding these risks. This review is intended to provide clinicians who use hyperosmolar therapy to manage intracranial hypertension with an evidence-based framework for the application of this management strategy.

Mannitol

Overview and Mechanism

Mannitol is a sugar alcohol ($C_6H_{14}O_6$) with a molecular weight of approximately 182 kDa, is not significantly metabolized, and is excreted unchanged in the urine. It is filtered at the glomerulus and is reabsorbed in the nephron, thereby acting as an osmotic diuretic. The half-life is affected by glomerular filtration rate (GFR) but averages from 39 to 103 min (dose 0.5 and 0.71/kg) [1].

Clinically, mannitol is used for diuresis in some forms of acute, oliguric renal failure, for reduction of refractory elevated intraocular pressure, and for reduction of elevated ICP. Although formal pharmacodynamic data is sparse, studies have suggested that the effects on ICP begin within minutes, peak between 15 and 120 min, and last from 1 to 5+ h [2–4]. The mean plasma half-life from intra-operative pharmacokinetic studies is 2.2–2.4 h [5, 6]. Mannitol is supplied in a variety of solutions ranging from 5–25% g/100 ml, with osmolality ranging from 274 to 1,372 mOsm/l, respectively.

Mannitol's primary mechanism of ICP reduction is by increasing the osmotic gradient across the blood–brain barrier (BBB), a structure across which it does not freely diffuse (low permeability coefficient) [7]. Mannitol's exclusion favors osmosis of water from the brain parenchyma, decreasing brain water content (BWC) and increasing extracellular volume. Reduction of BWC reduces perilesional edema, an effect that has been demonstrated in multiple clinical [8–10] and animal studies [11]. Mannitol works via additional, secondary mechanisms related to its favorable cardiovascular and rheological effects. Increased plasma volume [12] and subsequent decrease in hematocrit, viscosity [13, 14] and red blood cell deformability [14] improve flow through microvasculature [15] while enhancing cardiac output (CO) and mean arterial pressure (MAP) [16, 17]. Enhanced flow and cerebral oxygen delivery and subsequent cerebral vasoconstriction reduce cerebral blood volume (CBV), ICP, and increase cerebral perfusion pressure (CPP) [16–18].

Initiation of Therapy

Mannitol is effective for reducing raised ICP (Class II) [19] and is indicated in acute intracranial hypertension, as a temporizing measure when signs and symptoms are suggestive of active or impending transtentorial herniation (Class III) [19, 20]. There is no established ICP threshold above which mannitol therapy is indicated, and institutional variation still exists with regard to initiation, duration and monitoring of treatment. ICP-tailored treatment (with target ICP $>$ 25) is, however, more beneficial than symptomatic treatment alone [5, 16, 20, 21].

Using mannitol in patients with ICP $>$ 30 mmHg or with CPP $<$ 70 mmHg has been shown to yield statistically significant ICP reduction when compared to patient groups with ICP $<$ 30 mmHg or CPP $>$ 70 mmHg ($p < 0.001$) [4, 16, 22]. James et al. [21] demonstrated that, when stratified by ICP at onset of therapy, patients with higher ICPs exhibited a greater response than those with marginally elevated ICPs. In addition, the response to mannitol is likely influenced by number and amount of preceding doses; high cumulative doses are likely to yield diminishing returns [23]. These points suggest that administration of mannitol either prophylactically or outside of the context of acute ICP elevation may unnecessarily increase the total mannitol dose while providing marginal benefit to future ICP control, although this has not been empirically investigated.

Dosing

Reported doses of mannitol administered in the acute setting have ranged from 0.18 to 2.5 g/kg/dose, generally given as a 25% solution over 2–20 min. In 1977, ICP reduction was studied in a large series of patients with ICP $>$ 20 mmHg who received a total of 73 doses of mannitol in this range [22]. Ninety-six percent (96%) of patients "responded" (reduction in ICP of $>$10%).

The mean ICP reduction was 51.9%, the time to maximum reduction was 20–360 min ($x = 88$ min), and time to return to baseline ranged from 45 min to 11 h ($x = 210$ min). Unfortunately, specific dose–response data were not included in this investigation.

Numerous studies have suggested a dose–response relationship when using mannitol for ICP reduction. Doses less than or equal to 0.5 g/kg appear to be less efficacious and less durable [4, 21]. Several studies show more significant ICP reduction and more durable responses when doses between 0.5 and 1.5 g/kg are used [3, 4, 21]. Aggregate dose–response data from a 1980 series of 120 mannitol administrations for elevated ICP (at does from 0.18 to 2.5 g/kg) showed that 113 of 120 doses resulted in some response (10% reduction of ICP or greater), with the majority of non-responses occurring in the lower dose ranges: 0% response at 0.18 g/kg ($n = 1$), 25% response at 0.25 g/kg ($n = 4$), 78% response at 0.5 g/kg ($n = 9$), 99% response at 1 g/kg ($n = 86$), and 100% response at 1.5–2.5 g/kg ($n = 20$) [21]. A number of more recent trials also favor higher doses [24–26] of mannitol for managing elevated ICP. A recent randomized controlled trial (RCT) concluded that high dose (1.4 mg/kg) was preferable to conventional (0.7 g/kg) mannitol dosing in TBI patients [25]. This was preceded by a prospective RCT ($n = 178$) that demonstrated lower ICP, higher cerebral O_2 extraction, more frequent reversal of pupillary dilatation and better clinical outcomes at 6-month follow-up when high-dose mannitol was used preoperatively in the setting of acute subdural hematoma (SDH) [26]. The validity of these data remains in question, however, because of concerns regarding blinding of treatment and study groups [20].

A recent, comprehensive analysis of dose response data for mannitol confirms that the duration of its effects on ICP are dose-dependent [3]. These data show no significant difference in ICP reduction at 30-min post-infusion between patients given 50 and 100-g doses. However, at 60 min, patients treated with 50 g reached an ICP nadir, and pressures subsequently trended upward. At 100 min, the ICP in this group had almost returned to baseline (18.6 ± 7.6 mmHg). Conversely, the ICPs of patients treated with 100 g of mannitol remained low beyond 60 min (14.2 ± 6.7 mmHg, $P < 0.001$).

Monitoring and Titrating Therapy

Trends in serum osmolarity (S_{osm}) are often used to monitor and titrate mannitol dosing, and a "threshold" level of 320 mOsm, above which mannitol therapy should be decreased or withdrawn, is often set [27]. However, the sensitivity of S_{osm} for detecting or preventing renal failure has been questioned [28, 29], and an association between S_{osm} during mannitol therapy and acute renal failure remains unproven. A recent retrospective analysis of 95 patients treated with intermittent boluses of mannitol examined the association between serum electrolyte levels during therapy and development of ARF. In this study 11.8% of patients met the American Heart Association (AHA) criteria for acute renal failure. Patients in both the ARF and the non-ARF group had S_{osm} greater than or equal to 320, and the study demonstrated no independent association between S_{osm} and development of acute renal failure [28]. While these data do not necessarily obviate the role of monitoring S_{osm} in hyperosmolar therapy, they call into question the utility of the S_{osm} as a predictor of mannitol-induced acute renal failure and provide no evidence to support a S_{osm} threshold strategy for guiding mannitol therapy.

The osmolar gap (OG), which is the difference between the calculated serum osmolarity and the measured serum osmolarity, may be more representative of serum mannitol levels and its clearance [29]. OG is a stable value in both the normal and ICU populations, and its elevation correlates well with accumulation of serum mannitol [29]. In addition, lower OG is reflective of improved mannitol clearance and may indicate the safety of a subsequent dose [29]. Retrospective analyses of ARF case series data suggests that ARF occurring with an OG < 55 is exceedingly rare, with renal failure becoming more likely once OG exceeds 60–75 mOsmol/kg [30, 31]. Based upon this data, an OG threshold of 55 mOsm/kg has been suggested for monitoring hyperosmolar therapy for cerebral edema [2, 32, 33].

Given the above case reports, case series and retrospective analyses, it is reasonable to utilize the suggested 55 mOsm/kg as a threshold value, hence permitting the safe use of larger doses of mannitol between 0.5 and 1.5 g/kg. If monitored appropriately, mannitol-induced ARF is often reversible with cessation of the drug and will respond well to dialysis if necessary [30, 32]. Finally, limiting its administration in patients with CHF, high APACHE II scores, concomitant nephrotoxins or in the setting of acute or chronic renal failure are likely to reduce the risk of mannitol-induced acute renal failure.

Adverse Effects

Excessive systemic mannitol can cause acute renal failure, which has been reported following doses as low as 200 g over 24 h [1]. Other adverse effects include electrolyte abnormalities [11, 35], acidosis [35], hypotension [11, 16, 36], and congestive heart failure with pulmonary edema [33].

Renal Failure

Mannitol-induced acute renal failure (MI-ARF) is a well-described phenomenon reported in the setting of mannitol therapy for intracranial hypertension [1, 30–32, 37–41], but

the mechanism remains unclear. Microscopic analysis of the urine in patients with MI-ARF demonstrates vacuolated tubular cells consistent with "osmotic nephrosis;" however, this does not necessarily indicate permanent structural damage, as it is frequently reversible with cessation of the mannitol and/or initiation of dialysis [1, 30, 33].

The incidence of MI-ARF in patients with ICH, SAH, SDH, and stroke has been reported at rates ranging from 0 to 76%, with differences in the definition of ARF producing much of this variability [27, 28]. Defining ARF by what the AHA describes as a "useful working definition [42]" (an increase in serum Cr by $>$ 0.5 mg/dl for initial Cr $<$ 2.0 or by $>$ 1.0 mg/dl for initial Cr $>$ 2.0) categorizes a significant number of patients undergoing mannitol osmotherapy as having ARF. However, the risk of a clinically significant decline in renal function in these patients remains unclear. In a study of 51 patients receiving "low dose" mannitol osmotherapy (0.25–0.5 g/kg, stopped when serum osmolality reached 310 or greater), 76% of patients developed ARF by the AHA definition, yet none became anuric or oliguric and all Cr levels resolved by day 11 [27].

The mean reported total dose of mannitol administered over 2–5 days required to precipitate ARF in patients with previously compromised kidney function (295 $\pm$ 143 g) is significantly lower than the dose required in patients with previously normal renal function (1,171 $\pm$ 376 g) [1, 30]. A retrospective analysis of eight patients who developed ARF secondary to mannitol use for intracranial hypertension revealed an average mannitol dose of 189 g per day over multiple consecutive days with an average total dose of 626 g ($\sigma = 270$ g) [1]. Analysis of patient-specific data demonstrated that the lowest total mannitol dose causing ARF was 200 g over 1 day in a 42 year old with HTN and DM and a baseline creatinine of 1.4. The peak serum OG in this patient was 55 mOsm/kg, which has been noted as the threshold above which reduced GFR is likely to occur [2, 32, 33].

Assuming that the dose–response relationship with regard to nephrotoxicity is normally distributed within the overall population, the data above suggest that 97.5% of patients with normal baseline renal function will require a cumulative dose of $>$419 g mannitol to induce ARF. Extrapolating from this data, acute, one- or two-time dose(s) of even 2 g/kg of mannitol administered as temporizing measures during acute clinical decompensation should not precipitate ARF in the vast majority of patients. This is supported in several reports demonstrating that MI-ARF is limited to patients treated with $>$200 g/day [30, 32, 37]. Certain predisposing factors, including hypotension, sepsis, other nephrotoxic agents, or pre-existing renal disease, may confer additional risk of MI-ARF or may lower the cumulative toxic dose threshold in patients managed with hyperosmotic therapy [1].

Electrolyte Disturbances

Hyponatremia, hypochloremia, hyperkalemia, acidosis, elevated OG, and volume overload with associated pulmonary edema are the classic electrolyte disturbances seen with mannitol administration or intoxication [11, 30, 33, 35, 43]. Hyponatremia occurs during or immediately after infusion and begins to return to pre-dose levels as early as 30 min after termination of infusion [11]. The hyponatremia may be dose-dependent and may require up to 24 h to return to pre-dose levels with larger doses of mannitol (2 g) [11]. This hyponatremia does not clearly increase the risk of cerebral edema in the acute setting, post transfusion. However, prolonged uncorrected hyponatremia in the setting of mannitol-driven natriuresis may lead to worsening cerebral edema [37]. Conversely, prolonged mannitol administration with inadequate volume resuscitation may result in true hypernatremia in the setting of free water losses [34].

Transient decrease of serum bicarbonate also occurs immediately upon infusion of mannitol [35]. The mechanism is hypothesized to be secondary to intravascular dilution with bicarbonate-poor intracellular fluid shifts. This drop in bicarbonate is not associated with immediate academia, which only develops after more prolonged volume expansion. Statistically significant increases in serum potassium secondary to intracellular fluid shifts have also been described and have been associated with hyperkalemia-induced EKG changes [34, 35, 43].

Sequelae of Volume Expansion

Volume overload with associated pulmonary edema is a serious potential side-effect of mannitol administration [33]. Notwithstanding, exacerbations of CHF or pulmonary edema are rarely immediate or isolated effects of mannitol administration and are more typically seen in the context of pre-existing renal failure or cardiac dysfunction. Conversely, prolonged administration may result in diuresis and dehydration.

Acute Hypotension

Early prospective data in cardiac bypass patients suggested a positive correlation between hypotension and rapid administration of mannitol secondary to decreasing peripheral vascular resistance [44]. This same report showed a significant correlation between the rate of infusion and decreasing systolic blood pressure immediately (7–60 s) post-infusion in rabbits receiving 1 g/kg 25% mannitol solution. This phenomenon, which is generally not seen with a slower infusion (15–30 min) [16], has been validated in both animal studies and in human case series [16, 36].

Because acute hypotension in the context of elevated ICP can be associated with increased morbidity, theoretical concerns persist regarding rapid infusion of mannitol. However, a prospective RCT in pre-hospital TBI patients ($n = 41$) revealed no statistically significant drop in systolic blood pressure with administration of mannitol, when blood pressure was measured in 15 min intervals following infusion [45]. Given the clear evidence that 10–20 min infusions successfully reduce ICP [4, 16, 22, 24] avoiding rapid infusion (<5 min) may be advisable. However, there is no convincing evidence to suggest that rapid administration in the emergency setting is associated with adverse clinical outcomes.

Cerebral Perfusion and ICP Rebound

Another theoretical risk associated with mannitol is the phenomenon of "rebound" ICP increases. A proposed mechanism is that BBB leak creates a diminishing gradient that eventually may be reversed either iatrogenically or as the systemic solute is cleared. This theory has been supported primarily by data from in vitro [46] and animal studies [47–49]. Pharmacokinetic studies in dogs have shown that following supratherapeutic dosing, mannitol CSF concentrations rises to 66% of serum concentration in 2 h [11]. Rabbit models have shown a reduction in brain tissue water content but increasing CSF osmolarity, occurring 2-h post-infusion and lasting for hours after a single dose approximately equal to 2 g/kg in humans [48]. Pharmacodynamically, a feline model of cryogenic brain injury followed by five doses of mannitol showed exacerbation of cerebral edema with progressive accumulation of brain tissue and CSF mannitol, despite systemic clearance [49]. This has also been shown to occur preferentially in ischemic brain tissue in animals [47]. These preclinical data have fostered ongoing concern regarding a potential mannitol "rebound" phenomenon.

Leak at the site of damage of the BBB is a possible etiology [49–51]. Disruption of the BBB has been shown to result in mannitol accumulation in enhancing tumors and areas of infarct, recently confirmed utilizing in vivo magnetic resonance spectroscopy in the tumor and peri-tumoral area of a meningioma following a dose of 0.5 g/kg [50]. The extent of the clinical implications of this finding with regard to prolonged mannitol use, however, remains unknown.

Conversely, perioperative clinical studies at therapeutic doses show that CSF mannitol concentration achieves only 12% of the serum concentration 8-h post-infusion of a single dose (1 g/kg) [6], increasing from 1–5% over the first 4 h from intraoperative data [5] (as opposed to the 66% achieved from animal studies above in 2 h). In 1977 James et al. [22] reported that post-treatment ICP exceeded pre-treatment ICP by $\geq$10% in only 3 of 70 patients (4%), and additional details regarding these specific cases are lacking. Several other authors have reported no clinical evidence of rebound, suggesting that ICP elevation in the setting of hyperosmolar therapy may be secondary to post-mannitol water losses, hypovolemia and decreasing cerebral O_2, causing cerebral vasodilation and increasing CBV [16]. Maintenance of normovolemia could potentially prevent this outcome. Consequently, the magnitude and relative contributions of interstitial mannitol accumulation and changes in systemic water balance to the post-mannitol "rebound effect" remain unclear, however, growing evidence of mannitol brain tissue accumulation with repeated dosing may obviate the role of repeated mannitol administration in the setting of both cytotoxic and vasogenic edema.

Summary

In the setting of acutely elevated ICP, mannitol has been shown to reduce ICP and to improve CPP in a statistically significant, dose-dependant manner. Doses below 0.5 g/kg/dose are neither effective nor durable, and those above 2 g/kg/dose may be associated with increased nephrotoxicity, leading to a recommended dosage range of 0.5–1.5 g/kg/dose. Although there is no clear Class I evidence regarding clinically significant hypotension with rapid mannitol infusion, animal and human studies suggest that transient blood pressure reductions follow after rapid infusions (<5 min). Since infusion rates between 10 and 20 min per dose are safe and effective, it may reasonable to avoid rapid infusion unless the urgency of the clinical situation mandates immediate therapy.

Serum osmolarity is a relatively poor marker for titration of mannitol dose, and serum OG may be a more reliable and more clinically useful index for informing decisions regarding repeat administration or titration of mannitol therapy. Mannitol is generally well-tolerated even in this critically ill patient population, with transient electrolyte disturbances being among the most common side effects. Mannitol-induced ARF can occur and is more common with high doses, persistently elevated serum OGs, and in patients with comorbidities which themselves predispose to ARF. There is no Class I evidence to support concerns for clinically significant "rebound" ICP elevations in humans receiving mannitol therapy; however, there is laboratory and recent clinical evidence suggesting mannitol accumulation with prolonged therapy. The clinical implications of these findings remain undefined.

Hypertonic Saline

Overview and Mechanism

Hypertonic saline is effective in reducing elevated ICP in animal models [36, 52–57] and in humans with intracranial

hypertension associated with mass lesions [58, 59], TBI [36, 52–56, 60, 61], SAH [62–66], stroke [67, 68] and liver failure [69], and induced hypernatremia has been shown to correlate positively with CPP and negatively with ICP [70]. Although the neurotrauma guidelines task force found insufficient evidence to support or refute the preferential use of HTS in TBI over to the historical standard, mannitol. This was primarily due to a paucity of RCTs and to patient heterogeneity among otherwise strong retrospective studies. Notwithstanding, a growing body of evidence suggests that HTS may be more favorable than mannitol for elevated ICP, with a greater and more durable effect [36, 58, 59, 61, 71, 72].

Hypertonic saline is known to decrease ICP and increase CPP at least as effectively as mannitol [36, 53, 57–59]. This effect is achieved not only by its osmotic effect of decreasing intracerebral water content [52, 73] but also by its favorable hemodynamic properties (e.g., TBI with shock), including increasing ECF, CO, and MAP [60, 71, 74, 75]. These, in turn, increase CBF [52] and cerebral tissue oxygenation [60]. Cerebral tissue oxygenation may also be improved by the favorable effects of HTS on the microvasculature, where improved systemic microcirculatory flow occurs through reduced endothelial cell and erythrocyte edema [72, 76]. HTS also acts as an anti-inflammatory agent by decreasing leukocyte adhesion [77–79]. In addition, the regulated permeability of sodium across the BBB insures that an osmolar gradient will be maintained while presenting less theoretical concern for "leak" phenomenon, as quantified in its lower permeability coefficient [7].

Initiation of Therapy

Indications and timing for initiating therapy with HTS are less clearly defined than for mannitol. In the absence of clear recommendations, practices tend to vary by physician and by institution. Some physicians use HTS prophylactically in high risk patients to maintain supranormal serum sodium levels, while others use HTS only in the setting of acute herniation or to correct hyponatremia in brain injury patients. Often HTS is used as an adjunct therapy with mannitol, either sequentially or in combination [60, 74, 75, 80]. Notwithstanding, the relative safety and favorable properties of HTS have led some institutions to utilize it as first-line therapy. Class I evidence to recommend one strategy over another is currently lacking.

Dosing

Bolus dosage of HTS has been accomplished using concentrations varying from 3 to 23.4% [60, 66, 68]. There is little evidence to suggest superiority of one concentration over another, and consideration should be given to the total osmolar load being administered. While the total osmolar loads administered with boluses dosage of highly concentrated HTS (e.g., 23.4%) are often kept in the 200–300 mOsm/dose range [66] whereas less concentrated agents are used to deliver larger total loads (e.g., 3–10% HTS to deliver a total of 300–900 mOsm/dose [60, 68]), there is no particular evidence suggesting the necessity of this practice convention.

Dosing of infusion therapy of HTS has been effective using 3% NaCl at 0.1–2.0 ml/kg/h on a sliding scale titrating to serum sodium concentrations of 145–155^{+} [74, 81]. In addition, recent studies indicate that targeting $S_{osm} > 350$ mOsm/l provides clinically significant reduction in brain edema in the setting of stroke or mass lesion [73]. Clear guidelines and specific targets for an optimal serum sodium concentration are not well established.

Titrating and Monitoring Therapy

Infusion

A prospective, randomized, controlled study showed that a continuous infusion of 3% HTS administered over 72 h was effective in treating elevated ICP in pediatric TBI patients [82]. When compared head-to-head with a lactated ringer's infusion, the HTS patients experienced shorter intubation times, fewer complications (7 vs. 35%) and a shorter ICU stay. The data also demonstrate an inverse relationship between serum sodium and ICP as well as a direct correlation with CPP. A second study in pediatric patients also demonstrated a significant decrease in ICP spike frequency and an increase in CPP in patients managed with HTS infusion [83], supporting the use of HTS to decrease ICP in this population. Data of similar quality is lacking for the adult population.

Although limited, literature from the adult population suggests that the etiology of intracranial hypertension and the duration of therapy may affect the efficacy of HTS infusion therapy. Qureshi et al. [84] showed that HTS infusion reduced ICP in patients where the etiology of the elevated ICP was related to trauma or tumor edema but not for patients with ICH or stroke. They also presented imaging evidence of reduction in brain shift when HTS infusion was used in these selected patient groups, but their study suggested that this effect may not be durable beyond 72 h. The same authors later demonstrated that prolonged duration of HTS infusion (72 ± 85 h) was associated with a greater mortality (OR 3.1) and higher requirement for barbiturate coma [85]. While differences between treatment and control groups complicate interpretation of these studies to some extent, the literature may suggest that HTS infusion is capable of achieving ICP reduction for a period

<72 h but that this effect may not be durable with prolonged therapy [85].

Bolus

Bolus dosing of HTS is often used alone [79, 86, 87] or as an adjunct to continuous infusion therapy [81]. A bolus dose of 3% HTS (300 ml; 308 mOsm/dose) was shown to raise the mean serum sodium from 141 to 146 mEq/l within 20 min, with Na levels trending toward baseline at 60-min post-infusion [88]. In a separate study, a 4-ml/kg boluses of 7.5% HTS (14 mOsm/kg) increased serum Na by 11 mEq, and Na levels began to trend downward by 2-h post-infusion [83, 86]. In the setting of resuscitation from acute hypotensive episodes, HTS has yielded, at least equivalent, if not improved survival when compared head-to-head with lactated ringers solution and has been associated with few adverse events [54, 55, 89, 90]. The addition of dextran for durable intravascular expansion may [55, 87, 90, 91], or may not [89] improve survival. Adverse events with prolonged dextran use are possible; thus, dextran is not advocated by some [92]. Regardless of dextran utilization, HTS bolus dosing in trauma exerts beneficial hemodynamic and neuroprotective properties [54, 55, 87, 89, 90].

Bolus dosing has also been utilized to achieve ICP reduction in patients who are clinically refractory to mannitol therapy, and this strategy has been shown to produce additional reduction in ICP, elevation in CPP, and increases in cerebral tissue oxygenation without additional side effects [60]. These effects were demonstrated using 250 ml boluses of 7.5% HTS administered over 30 min (641 mOsm/dose) [60], but additional studies have reported bolus dosages of 30 ml of 23.4% HTS (240 mOsm/dose) [66] and 75 ml of 10% HTS (342 mOsm/dose) [68] with similar effects. Bolus dosage of HTS has been shown to temporarily reverse transtentorial herniation in these patients [10, 57]. In addition, clinical data suggest that HTS conveys at least equivalent, if not greater efficacy than mannitol when administered as a bolus dose, and reduces ICP in patients even when mannitol has failed [60, 66, 75].

Adverse Effects

A retrospective analysis of adverse drug reaction data from Austria between the years 1991 and 2000 found only four adverse reactions in over 18,000 patients treated with HTS therapy [93]. The hyperosmolar state can cause renal failure and its sequelae, in addition to electrolyte abnormalities secondary to fluid shifts and hyperchloremia [94]. In addition, hypernatremia in the setting of hyperosmolar therapy Na > 160 mEq/l has been independently associated with increased mortality in NICU patients [95].

Several theoretical concerns regarding complications such as thrombophlebitis, tissue ischemia, or deep vein thrombosis associated with HTS infusions are often cited but not clinically relevant with appropriate administration [88, 93, 96]. In addition, concern for central pontine myelinolysis, which can be observed in the clinical context of aggressive correction of hyponatremia in malnourished or chronic alcoholic patients, is hypothesized but is not reported in the setting of induced hypernatremia in normonatremic patients for the treatment of intracranial hypertension [93, 97, 98].

Renal Failure

To avoid renal complications, hyperosmolar therapy in TBI patients is commonly limited to S_{osm} levels of 320–330 mOsm/l and Na of 155–165 mEq/l [20]. However, a randomized trial in pediatric TBI patients reported average peak S_{osm} levels of 364.8 mOsm/l and average peak Na levels of 170.7 mEq/l [83]. Two of ten patients in this study developed renal failure in the context of concurrent sepsis; and, although there is no clear evidence that hyperosmolar therapy precipitated their ARF, their peak serum sodium levels did reach 181 and 186 mEq/l. Conversely, a third patient exceeded a sodium level of 180 mEq/l without evidence of renal dysfunction [83]. A subsequent review of 68 pediatric patients demonstrated a correlation between rising creatinine and increasing serum Na and S_{osm} levels, yet no patient developed renal failure despite an average S_{osm} of 331 mOsm/l [99]. These data have prompted the pediatric TBI guidelines to include the "option" of HTS 0.1–1 ml/kg infusion targeting S_{osm} < 360 mOsm/l rather than the <320 mOsm/l as with mannitol [100].

Similarly, a retrospective study in adult patients compared 3% HTS to normal (0.9%) saline infusions in patients in a neuro-critical care setting [96]. Patients at risk for developing intracranial hypertension with Na < 140 mEq/l were treated empirically with 3% HTS (for at least 24 h, mean 6 days at 1.5 ml/kg). Although there was the expected, statistically significant increase in serum sodium and a concurrent trend toward elevations in serum creatinine and blood urea nitrogen in the HTS group, the relative risk for developing ARF was not increased. Taken together, these data suggest that ARF is an infrequent complication of HTS therapy and that serum Na and S_{osm} levels above 145 mEq/l and 330 mOsm/l are not necessarily associated with an increased risk of renal complications.

Electrolyte Disturbance

Induced hypernatremia is associated with several other electrolyte disturbances. A transient hypokalemia commonly results immediately following infusion [88, 94],

although it tends to return to baseline by 1-h post-infusion [88]. When compared to normal saline, 4 ml/kg of 7.5% HTS will significantly increase serum sodium (+11 mmol/l) and chloride (14 mmol/l) and decrease potassium (−0.1 mmol/l), which tends to increase by 1-h post-infusion (+0.3 mmol/l) [94]. Hyperosmolar also expands ECF and intravascular volume with bicarbonate-poor intracellular fluid, reducing serum bicarbonate and a resulting in a temporary but statistically significant decline in pH [94]. This effect may be more pronounced with HTS than with mannitol [69], but decreases in pH observed at 20-min post-infusion generally return to baseline by 60 min. Lactate levels also decline throughout this period [88], presumably attributable to improved tissue perfusion secondary to the augmentation of CO, MAP, and microcirculatory flow observed in HTS resuscitation studies [72, 76–79]. Although both mannitol and HTS may lower pH, in animal models, HTS does so to a greater extent [58]. The diuretic effects with prolonged use require monitoring of electrolytes and fluid balance to avoid clinically significant electrolyte abnormalities.

Central Pontine Myelinolysis

Central pontine myelinolysis (CPM) is a frequently discussed but primarily theoretical concern associated with hyperosmolar therapy. CPM is known to occur in the setting of rapid correction of the hyponatremic state [97], particularly in patients who are chronically malnourished or alcoholic. Reports of CPM in normonatremic patients rapidly treated to and maintained in a hypernatremic state are rare, and evidence suggests that sodium increases of 20 mEq over 15 min with bolus infusions are well-tolerated and begin to trend down within 60 min [88, 93, 101].

Data supporting the concern for CPM in normonatremic patients are derived primarily from animal models. For example, Soupart et al. demonstrated that normonatremic rats treated intraperitoneally with 20 ml/kg of 11.68% NaCl solution experienced rapid increases in serum sodium (from 139 to 167 mEq/l in 6 h and to 174 mEq/L in 12 h) and subsequently developed symptoms of muscle twitching and spasm. 47% progressed to coma and death within 12 h [98]. It is worth noting here that initial bolus doses of 20 ml/kg of 11.68% NaCl exceeds the typical bolus dosages of HTS administered in the clinical setting by more than 10-fold. It is also unclear if the deaths were truly attributable to CPM.

In vivo there is only one, unconfirmed report of CPM when treating TBI when a large (>1l) infusion of 7.5% HTS/7.2% HES was mistakenly administered in under 7 h, once again in significant excess of standard dosing. This patient developed spastic tetraparesis and was given the diagnosis of "pontine myelinolysis," but neither histologic confirmation nor detailed data regarding serum sodium levels were reported [94]. Moreover, studies where high osmotic loads or sodium levels have been introduced appropriately have not reported clinical, radiographic, or pathologic evidence of CPM [70, 84, 99, 101].

Acute Red Blood Cell Lysis

A common concern when HTS is administered (particularly peripherally) is precipitation of intravascular red blood cell lysis. This concern was initially reinforced by data reported from bled dogs [102], but this data is not likely to be directly applicable to humans because, unlike most mammals (including humans), dogs RBC plasma membranes are deficient in Na/K ATPase [103]. In addition, in vitro analysis reveals no evidence for hemolysis with human RBCs [104].

Infusion Phlebitis and Regional Necrosis

Common clinical practice at many institutions is to require central venous access prior to infusion of hypertonic solutions in order to prevent phlebitis, septic thrombophlebitis, or regional necrosis. There is little empiric data available to either support or refute this practice, and there is no definitive evidence to support a particular osmolality threshold value above which central venous access is required. More importantly, while prolonged peripheral infusions of hyperosmolar fluids are associated with increased peripheral vascular complications, there is no data to suggest that acute therapy with HTS should be postponed in order to achieve central venous access.

Data regarding prolonged hyperosmolar solution infusion can be found in nutrition literature, where total parenteral nutrition (TPN) solutions are frequently hyperosmolar. The thrombophlebitis rate with peripheral venous infusions of 829 mOsm solutions over 24 h was ~ 4% at 48 h increased to 14% after 14 days. Infusion of 1,044 mOsm solution resulted in rates of 27 and 73%, respectively [105]. Continuous infusions over 48 h to 2 weeks show a statistically significant and dose-dependent relationship, suggesting that prolonged peripheral administration of hyperosmolar fluids may be relatively contraindicated.

Bolus dosing, particularly in the acute setting, confers much lower rates of phlebitis. Animal data from infusions of 7.5% NaCl/6% dextran-70 into bled sheep via cephalic venous access demonstrate no histologic evidence of venous damage after bolus administration [106]. Human studies have also revealed no complications associated with pre-hospital bolus administration of HTS in 48 hypotensive penetrating trauma patients [107]. In addition, a multi-center review of 359 patients receiving pre-hospital HTS (7.5% NaCl/6% dextran-70) versus lactated ringer's

demonstrated no peripheral vascular complications secondary to HTS administration [108]. Together, these data suggest that rigid adherence to protocols requiring central venous access prior to administration of HTS, particularly in the acute setting, are not supported by current evidence. Prolonged, peripheral use of HTS may confer additional risk of local complications, and central venous administration may reduce local complications in this setting.

ICP Rebound

As with mannitol, concerns persist regarding rebound intracranial hypertension following hyperosmolar therapy with HTS. Empiric evidence of this phenomenon occurring after hyperosmolar therapy with HTS is even less convincing than with mannitol and is limited to individual reports and small series [80, 109, 110]. For example, Qureshi et al. reported two patients with intracerebral hemorrhage whose exams improved after 24 h of 2% HTS therapy. After 5 days, the infusions were discontinued and both patients deteriorated on day 8 secondary to worsening cerebral edema which was again reversible with HTS [109]. This report provides no evidence to delineate "rebound" ICP elevation from persistent cerebral edema compounded with cessation or rapid correction of the hyperosmolar state, which may precipitate ICP exacerbations. Clear evidence to support or refute this phenomenon is therefore lacking.

Summary

Hyperosmolar therapy with HTS is one of the few existing therapies shown by prospective controlled trials to improve survival in patients with elevated ICP associated with TBI [100]. Some conflicting evidence does persist in the literature [85]. Current evidence does not demonstrate an elevated risk of developing renal failure with serum sodium concentrations less than 155 mEq/l [96], and it is unclear whether higher sodium concentrations (155–170 mEq/l) and osmolarity <360 mOsm/l are associated with clinically significant complications or simply correlate to transiently elevated BUN/Cr. Bolus dosing guidelines are not clearly defined and appear in various formats, including volume/dose, ml/kg and mOsm/kg. Current data shows boluses ranging from 200 to 641 mOsm/dose to be safe, to be at least as effective as equiosmolar doses of mannitol as the primary therapy, and to be useful when initial therapy with mannitol has failed [60, 83, 86, 111, 112]. Dosing and administration protocols for infusion therapy are comparably undefined; but, regardless of the infusion protocol, therapeutic hypernatremia combines a favorable risk/benefit profile with demonstrated efficacy for ICP reduction and CPP augmentation in the setting of intracranial hypertension.

Adverse reactions, such as electrolyte abnormalities and the possibility of thrombophlebitis, appear to be mild, transient, and often preventable with appropriate ICU management and infusion. CPM has not been reported in patients treated with the typical concentrations and dosage regimens of HTS, and there is little compelling evidence for "rebound" ICP increases unless prolonged hyperosmolar therapy is rapidly discontinued or reversed. Concern regarding peripheral thrombosis and thrombophlebitis, as well as fear of rapid RBC lysis following peripheral bolus infusion of HTS are not supported by in vivo, human data. While extrapolation from literature regarding TPN suggests that central venous infusion may reduce the risk of peripheral vascular complications associated with prolonged infusions of HTS, there is no direct evidence to support or refute this believe. More importantly, there is no evidence to suggest that central venous access is required for bolus administration of HTS, particularly in the acute setting.

Mannitol versus HTS

Animal studies comparing mannitol and HTS suggest comparable safety and efficacy [34]. A 1993 study using a sheep model of head injury compared 250 ml of 7.5% HTS to 250 ml of 20% mannitol, and no statistical difference was found between the two agents with regard to changes in MAP, HR, UOP, serum pH, ICP, and CPP. Reduction of BWC was equivalent in both groups, and safety of the two agents was found to be equivalent [58]. Conversely, rodent models of brain injury [53], ischemia [47], and SAH [56, 113] have suggested superior effect of HTS. In a canine model of ICH utilizing autologous blood injection, equiosmolar doses of mannitol (1 g/kg), 3% HTS (5.3 ml/kg), and 23.4% HTS (0.7 ml/kg) demonstrated that all three agents achieved prompt ICP reduction, although the degree of reduction was greater in the HTS groups. At 120 min, the 3% HTS had a statistically lower ICP than the other two agents, and HTS resulted in lower BWC and a higher CPP versus mannitol [59]. Mechanism of injury is likely to be at least partially responsible for these differences, and Mirski et al. [53] hypothesized that variables recorded in anesthetized animals may not reflect clinically relevant physiology.

While the data from animal models suggests that mannitol and HTS generally have comparable physiological and clinical effects when administered at equiosmolar doses, the variability in the details of the results demonstrate the critical role of human, in vivo analyses. Several recent studies have shown that equiosmolar doses of HTS and mannitol have similar efficacy when used as initial monotherapy for elevated ICP in humans[115] and that

HTS decreases ICP when mannitol fails[60, 83, 86, 111, 112]. A recent prospective clinical trial highlighted the comparison of equiosmolar doses of 20% mannitol and 7.45% HTS (255 mOsm; 230 and 100 ml, respectively) [116]. At 60 min from the start of infusion the ICP in both groups was significantly reduced (45 and 35%, respectively), with no statistically significant differences in the degree of ICP reduction between the two agents. In TBI patients, 7.5% HTS (2 ml/kg, 361mosm/dose) was found to outperform 20% mannitol (0.45 g/kg, 175 mosm/dose), with a greater failure rate and a greater frequency/duration of ICP elevation in the mannitol group [61]. A recent randomized, controlled, cross-over trial comparing 200 ml of 20% mannitol to 100 ml of 7.5% HTS/6% dextran found the ICP reduction in the HTS group to be greater and more durable than the mannitol group [115]. Finally, a review of studies in cases of ICP refractory to mannitol suggested that doses of 250 ml of 7.45% HTS (641 mOsm/dose) ranging from 240 to 641 mOsm/dose were safe and were effective at achieving ICP control when mannitol had failed [83, 86, 113].

Intraoperative evidence in humans suggests that HTS provides superior brain relaxation to mannitol [117], and a recent meta-analysis of 36 human studies involving HTS for ICP reduction (including some of those investigations discussed above) suggests that HTS may have superior overall efficacy (relative to mannitol) in reducing elevated ICP [118]. A similar meta-analysis of five, randomized clinical trials addressing this question calculated the overall relative risk of ICP control with HTS versus mannitol to be 1.16 (95% confidence interval 1.00–1.33) with a mean improvement in ICP control of 2.0 mmHg in patients treated with HTS relative to those treated with mannitol [119].

All of these studies, however, note that higher quality data is necessary to address this issue definitively. Unfortunately, several barriers to large-scale, head-to-head trials remain. Foremost, the heterogeneity of treatment algorithms across institutions makes direct comparisons difficult. In addition, unique clinical situations related to the diverse etiologies and mechanisms of intracranial hypertension, neurological and systemic comorbidities present in patients with elevated ICP, and variable clinical contexts in which hyperosmolar therapy is initiated and maintained further complicate direct comparisons [119]. Finally, most trials currently consider ICP reduction as the primary outcome metric under study. While ICP reduction is often assumed to be associated with clinical outcome, additional, head-to-head trials specifically focusing on patient outcomes as a function of ICP reduction with HTS and mannitol therapy need to be conducted in order to measure this presumptive relationship.

Conclusions

Clinical evidence demonstrates the efficacy of mannitol and HTS for acute intracranial hypertension in the setting of TBI, tumor edema, ICH, SAH, and stroke [57, 59, 61, 67, 68, 80, 114]. Class I evidence for initiation, dosage, monitoring and titration of these hyperosmolar agents, however, is lacking. Both mannitol and HTS are shown to lower ICP by a variety of mechanisms, including osmotic dehydration of brain interstitium (non-injured) [8, 9, 52, 73, 110, 114], reduction in blood viscosity [13, 76–79], increasing RBC deformability [14, 72, 76], improving CO (including increased CO, MAP) [16, 17, 71, 74, 75] and microcirculatory flow [15, 72, 76–79]. These effects result in net improvements of brain perfusion despite reduction in CBV [16, 17, 52, 60]. Additional anti-inflammatory mechanisms reducing leukocyte adhesion [77–79] and endothelial cell edema [72, 76] have also been shown for HTS.

Initiation of therapy in an ICP- and CPP-directed manner is shown to be effective, especially when ICP $>$ 30 and CPP $<$ 70 [4, 16, 20–22]. This approach achieves ICP reduction while reducing risks associated with increasing cumulative doses of these agents. Mannitol dosing has been suggested between 0.18 and 2.5 g/kg, although doses $<$ 0.5 g/kg are less efficacious and less durable [3, 4, 21], and a positive correlation has been demonstrated between dose and magnitude of ICP reduction [3, 21, 24–26]. Bolus dosing of HTS (in concentrations ranging from 1.5 to 23.4%) can be generalized as ranging from 240 mOsm/dose (e.g., 30 ml of 23.4%) to 640 mOsm/dose (e.g., 250 ml of 7.5%). In a 70-kg patient, these concentrations equal $\sim$3.4 to 9 mOsm/kg/dose.

The majority of the adverse effects of hyperosmolar agents, including electrolyte disturbance, volume overload, acute hypotension, are subacute and are avoidable with appropriate monitoring and with aggressive supportive care. The dose-limiting effect of hyperosmolar therapy appears to be its effects on renal function. This is especially true with mannitol, where administration of as little as 200 g over a 24 h period may potentially precipitate MI-ARF (although the average, cumulative nephrotoxic dose in patients with normal renal function are 1,171 $\pm$ 376 g) [1, 30]. Monitoring serum osmolarity in these patients does not appear to predict the development or risk of ARF [28], but monitoring the difference between the calculated and measured serum osmolarity (the OG) is more predictive [2, 32, 33]. Current literature suggests a threshold OG of 55 mOsm/kg [2, 27, 30–32, 37].

Rebound ICP increase has been reported with hyperosmolar therapy (particularly with mannitol), but is not clear whether this is secondary to iatrogenic reversal of the

hyperosmolar gradient or whether true spontaneous reversal takes place. Concerns of CPM are generally unfounded in normonatremic patients receiving hyperosmolar therapy for elevated ICP [88, 93, 101]. Concerns for red blood cell lysis are similarly unsubstantiated [104]. Infusion phlebitis and vascular necrosis, although possible with long term, peripheral administration [105], are not reported with acute administration of hyperosmolar agents and have not been substantiated in animal [106] or in human studies [96, 107, 108]. These findings suggest that central access is not required for bolus or short-term hyperosmolar therapy, and there is no evidence that potentially life-saving treatment with hyperosmolar agents should be deferred in favor of central vascular access.

Head-to-head trials have recently suggested that HTS may be more effective in reducing ICP than mannitol, but the magnitude of this difference and the clinical implications remain unclear. There are a number of barriers to providing irrefutable data from direct comparisons of these agents, including variable etiologies of intracranial hypertension, variable institutional and practice parameters regarding hyperosmolar therapy, inconsistent reporting of premorbid conditions, and challenges correlating ICP reduction with clinical outcomes. Additional research is needed to demonstrate definitive superiority in effectiveness of these hyperosmolar agents.

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