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Essay

Mannitol versus hypertonic saline solution in neuroanaesthesia☆

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ABSTRACT

Background: Hyperosmolar therapy with mannitol or hypertonic saline solution is the main medical strategy for the clinical management of intracranial hypertension (IH) and cerebral oedema. IH and cerebral oedema are usually the result of acute and chronic brain injuries such as severe head trauma, ischaemic stroke, intracerebral haemorrhage, aneurismal subarachnoid haemorrhage, tumours and cerebral infections.

Objective: We conducted this research in order to assess the benefits and side effects of osmotherapy and to identify the current trends in the management of IH and cerebral oedema. These two conditions worsen neurological outcomes and are the major cause of mortality in neurological patients.

In this article we show the current evidence supporting the use of HTS and mannitol, and examine the question of which of the two agents is considered the best option for the medical treatment of IH. We review the efficacy data for HTS compared with mannitol in terms of clinical considerations.

Conclusion: Data availability is limited because of small sample sizes, inconsistent methods and few prospective randomized comparative studies, although both agents are effective and have a reasonable risk profile for the treatment of cerebral oedema and IH. Currently, several trials show that HTS could be more effective in reducing ICP, with longer lasting effects. HTS maintains systemic and cerebral haemodynamics.

Abbreviations: SAH, subarachnoid haemorrhage; IH, intracranial hypertension; HTS, hypertonic saline solution; CSF, cerebrospinal fluid; Cr, serum creatinine; M, mannitol; ARF, acute renal failure; PDBRT, prospective randomized double-blind trial; PRCT, prospective randomized controlled trial; ICP, intracranial pressure; TBI, traumatic brain injury; DVT, deep vein thrombosis; AVM, arterio-venous malformation; N-ICU, neurosurgical intensive care unit; CBV, cerebral blood volume.

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Manitol versus solución salina hipertónica en neuroanestesia

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RESUMEN

Antecedentes: La terapia hiperosmolar con manitol o solución salina hipertónica (SSH) es la principal estrategia médica para el manejo clínico de la hipertensión intracraneal (HIC) y del edema cerebral. La HIC y el edema cerebral suelen ser las consecuencias de lesiones cerebrales agudas y crónicas tales como el trauma craneoencefálico severo, el accidente cerebrovascular isquémico, la hemorragia intracerebral, la hemorragia subaracnoidea aneurismática, y los tumores e infecciones cerebrales. Ambas entidades, contribuyen a peores resultados neurológicos y producen mayor mortalidad en los pacientes neurocríticos.
Objetivo: Realizamos esta investigación con el objetivo de valorar lo efectos beneficiosos y secundarios de la osmoterapia y cuáles son las tendencias actuales para el manejo de la HIC y del edema cerebral. En el presente artículo mostramos la evidencia actual que soporta a la SSH y al manitol y cuál se considera la mejor opción como terapia médica en el tratamiento de la HIC. Revisamos la eficacia de los datos para SSH frente a manitol hablando sobre sus consideraciones clínicas.
Conclusión: La disponibilidad de los datos es imitada por las muestras pequeñas, métodos inconsistentes y pocos estudios aleatorizados prospectivos comparativos, y aunque ambos agentes son eficaces y tienen un perfil de riesgo razonable para el tratamiento del edema cerebral y en la HIC, en la actualidad varios ensayos demuestran que la SSH podría ser más eficaz en la reducción de la PIC y por más tiempo. La SSH mantiene la hemodinamia sistémica y cerebral.

Introduction

Several studies in animals and humans have demonstrated the efficacy of hyperosmolar agents in lowering ICP, produce plasma expansion, change the blood rheology and have anti-inflamatorios.[1] However class I literature to support the use of these agents is variable, and this is due to the heterogeneity of the etiology of ICH, associated comorbidities, the choice of drug, dosage and methods of monitoreo.[1]

Mannitol is an osmotic agent management of ICH since the 1960s. But it was not until 1962, where it is used in the clinic for the first vez.[2,3] Not cross the intact cell membrane or blood brain barrier (BBB). Therefore, in the brain, remains in the vascular fluid compartment and thus removes the intracellular space and intersticial.[2,3] Countless studies show its effectiveness in reducing ICP, and at least one study showed that mannitol reduced mortality in patients with IH due to TBI, compared with the use of barbiturates.[4,5]

Hypertonic saline solution was used in a clinical application for the first time in 1926 by Silver who used 5% HTS for the treatment of Burger's disease.

Regardless of its aetiology, intracranial hypertension creates a secondary lesion because it lowers CPP, predisposing the brain to ischaemia and triggering brain tissue displacement with the risk of compressing vital structures.

Conventional strategies for the management of patients with IH range from pharmacological therapies to surgical interventions.

The primary objective of these measures is to maintain adequate CBF in order to meet neuronal metabolic needs and prevent cerebral ischaemia. Regardless of the aetiology of IH, osmotherapy is one of the pillars in the management of this disorder.

Cerebral oedema results from increased water content in the brain, and most cases of brain injury with IH begin in the form of focal cerebral oedema. Traditionally, oedema is classified as cytotoxic, vasogenic and interstitial. In most cases, it is usually mixed. Vasogenic oedema is usually the result of increased capillary permeability due to breakdown of the BBB from trauma, tumours, abscesses, white matter usually being the most affected. In contrast, cytotoxic oedema is defined as swelling involving neurons, glia and endothelial cells due to an energy failure that affects both the grey and the white matter; it happens when there is water accumulation in the cytosol as a result of deranged osmolyte distribution. Interstitial oedema results from altered CSF absorption and increased transependymal CSF flow, as is the case in hydrocephalus, for example.[6]

There is current evidence in the experimental and the clinical literature in the sense that HTS is an effective alternative to conventional osmotic agents in neurocritical patients with different aetiologies.

The first idea of osmotherapy for CNS diseases came about in 1919 when two research fellows from Reed Army Medical Centre working at Johns Hopkins medical school observed that the intravenous injection of 30% saline solution in anaesthetized cats led to a 3–4 mm reduction in brain size, lasting 15–30 min after each injection.[7] However, the injection of hypotonic solutions created brain herniation through the craniotomy site. Fremont-Smith and Forbes in 1927, and Javid Settlage in 1950,[8] began using intravenous injections of

concentrated urea, but its use was abandoned due to several disadvantages such as clinical toxicity, instability of the preparation, time to make the preparation, and rebound effect on ICP. By 1962, Wise and Carta reported their experience using 20% and 25% mannitol, including longer duration, good ICP control, smaller rebound effect, greater product stability, low cost and absence of toxicity.[9]

During the 1980s, beneficial effects using small HHS boluses were shown in resuscitation in trauma, both in humans as well as in animal studies. Effects on the brain were shown by Todd in 1985 after causing isovolemic haemodilution for 1 h using hypertonic Ringer's lactate with Na 252 mEq/l and 480 mOsm/l osmolality in rabbits under anaesthesia and ventilation, with no brain lesion. They observed a lowering of ICP and of the total volume of water in the brain, improving CBF.[10,11]

Mannitol

Mannitol is a sugar alcohol with a molecular weight of 183 kDa. It is filtered in the glomeruli and reabsorbed in the nephron as an osmotic diuretic, it is hardly metabolized, and it is excreted unchanged. Its plasma half-life is 2.2–2.4 h as determined by intraoperative pharmacokinetic studies,[12,13] the onset of action occurs within 15–20 min, and its maximum effect on the brain occurs 30 min after administration and lasts from 90 min to 6 h depending on the aetiology. The usual indications include lowering of refractory IOP, elevated ICP, oliguria, and some forms of ARF. It acts on ICP 15–20 min after administration, optimizing the rheological properties of blood by reducing its viscosity, lowering the haematocrit, and increasing CBF and O_2 supply. This results in reflex self-limiting regulation vasoconstriction of cerebral arterioles, leading to reduced cerebral blood volume and ICP, and to increased CPP.[14,15] Consequently, the primary mechanism by which mannitol reduces ICP is by increasing the osmotic gradient through the BBB (a structure which does not diffuse freely because of its low permeability coefficient).[16] It also leads to reduced systemic vascular resistance (and afterload), combined with a transient increase in preload and a mild positive inotropic effect, improving cardiac output[17] and O_2 transport. However, intravascular volume usually drops due to mannitol's diuretic effect, which may lead to a drop in BP and to haemodynamic instability. Fluid replacement is required to avoid hypovolemia and subsequent secondary ischaemia or ICP elevation from reflex vasodilation of cerebral arterioles. Mannitol is used in a variety of solutions ranging from 5% g/100 ml to 25% g/100 ml with an osmolality between 274 and 1.372 mOsm/l.[18]

Mannitol is an effective way to lower ICP elevation (Class II)[19] and it is indicated in acute intracranial hypertension as a measure to be assessed when there are signs and symptoms of active or impending transtentorial herniation (Class III).[19,20] There is no established ICP threshold above which mannitol therapy is indicated. Treatment with objective monitoring when ICP >25 mmHg is more beneficial than symptomatic treatment.[20,21]

Several studies show that if ICP is >30 mmHg with a CPP <70 mmHg a significant reduction is obtained compared with ICP <30 and CPP >70 mmHg, with a $p = 0.001$.[22,23]

As far as dose is concerned, ICP reduction and longer lasting responses have been observed when a dose between 0.5 and 1.4 g/kg is administered.[24] Infusions must be given over a period of approximately 20 min. Faster infusion rates (<5 min) have been shown to be associated with transient arterial hypotension.

The goal of osmotherapy is to maintain normovolemia or slight hypervolemia, but maintaining serum osmolality between 300 and 320 mOsm/l; this requires monitoring during the therapy.[25,26] The osmolar gap is the difference between calculated and measured osmolality. An elevated osmolar gap correlates with mannitol accumulation, and a low level ensures mannitol clearance.[26] Moreover, the osmolar gap indicates that additional doses may be used later without the risk of ARF, considering that a retrospective data analysis showed that at an osmolar gap <55 ARF is rare. The highest probability of ARF is found at levels of 60–75 mOsm/kg.[27,28] Several studies have shown that more than 200 g/day are required to produce ARF and that ARF can usually be reversed when the substance is interrupted.[29] Other adverse effects include electrolyte disturbances,[30] acidosis,[30] hypotension,[31] and congestive heart failure with pulmonary oedema.[32] The most frequent disorders with the use of mannitol include hyponatremia, hypochloremia, hyperkalemia, acidosis and volume overload associated with pulmonary oedema.[32]

The most significant risks associated with the use of mannitol are ARF and the rebound phenomenon with increased ICP. The mechanism proposed to explain this phenomenon is the loss across the BBB which creates a decreasing gradient that may eventually be reverted.[33–36] Studies in dogs showed that, after overdosing mannitol, the concentration in the CSF increased after 2 h of the infusion.[36] The study in rabbits showed a reduction in cerebral water content but increased CSF osmolality 2 h after the infusion, which was prolonged after a single dose of 2 g/kg.[37] The loss of BBB continuity has been demonstrated by the observation of mannitol accumulation in tumours and in stroke areas using magnetic resonance spectroscopy after a dose of 0.5 g/kg. Some authors have not reported any clinical evidence of rebound suggesting an increase in ICP, but Rosner published in 1987 an article reporting that water loss after mannitol administration produces hypovolemia, lower cerebral O_2 leading to vasodilation, and an increase in cerebral blood volume.[23] In conclusion, there is evidence of the size of interstitial accumulation and systemic changes in water balance after the use of mannitol; however, the rebound phenomenon is uncertain, although evidence suggests that accumulation increases. ARF associated with the use of mannitol has been described, but its mechanism is unclear. The American Heart Association defines ARF as an increase of 0.5 mg/dl in serum creatinine; Cr < 2.0 or >1.0 mg/dl; or creatinine > 2.0. Microscopic urinalysis has revealed vacuoles in tubular cells consistent with osmotic nephrosis, which generally does not result in permanent injury and reverts after the drug is removed. Several studies report that the lowest total dose of mannitol that may cause ARF is >200 g/day. It is important to note that in patients with impaired renal function the total dose of mannitol that

may cause ARF may be lower than that in patients with normal renal function. Several factors need to be considered when mannitol is started, including hypotension, sepsis, and the use of other nephrotoxic agents given the additional risk of lowering the threshold of the toxic dose accumulated in the patient.[18]

Hypertonic saline solution

In recent years, hypertonic saline solution has become the most popular osmotic agent for hyperosmolar therapy. This growing popularity has come about in response to the complications associated with the use of mannitol, in particular ARF and ICP rebound, because although it is not clear whether it worsens the neurological outcome, it is still an important concern. HTS comes in different concentrations – 2%, 3%, 7.5%, and 23.4% – and the recommendation is that if it needs to be used at a >2% it must be delivered through a central line, thus avoiding the risk of thrombophlebitis and peripheral vein thrombosis; bolus doses result in a lower rate of phlebitis. Data in animals using infusions with 7.5% HTS, 6% NaCl and 6% dextran through the cephalic vein did not show any evidence of histological venous damage after bolus administration.[38] In 1991, Maningas showed that there were no complications associated with bolus administration in 48 patients with penetrating trauma in the pre-hospital setting.[39] A multi-centre study of 359 patients receiving HTS before arriving at the hospital (7.5% NaCl, 6% dextran 70) versus Ringer's lactate did not show peripheral vascular complications secondary to HTS administration.[40] There is no current evidence for protocols requiring venous access for HTS administration, particularly in the acute phase.

Indications include lowering ICP in patients with TBI,[41–45] sub-arachnoid haemorrhage,[46–49] stroke,[50,51] liver failure,[52] and also as adjunct therapy with mannitol, either sequentially or in combination.[43]

It is not yet clear if it must be a bolus dose or an infusion. The bolus dose has been used at different concentrations with no evidence of superiority of any concentration in particular, but consideration must be given to total osmolar load. Infusions have shown to be effective with 3% HTS at a rate of 0.1–2 ml/kg/h, with step-wise titration of the dose to a target of 145–155 mEq/l NA+ (maximum 160 mEq/l) and an osmolality of 320–330 mOsm/l (maximum 360 mEq/l). The literature suggests that HTS infusion lowers ICP over a period <72 h, but this effect cannot be maintained with prolonged therapy.[18] The bolus dose is used alone or as a complement to continuous infusion therapy. It is also used to lower ICP in patients who have not responded to prior mannitol therapy, and this measure further reduces ICP, raises CPP and increases brain tissue oxygenation without adding side effects.[18]

There are no pharmacokinetic data on HTS, but Lazaridis suggests that the onset of the effects is similar to that of mannitol.[53] Its action is similar to that of mannitol in that it elicits water outflow from the nervous tissue towards the intravascular space and reduces the rate of CSF production, thus improving intracranial compliance; it has a lower diuretic effect, hence the initial advantage of expanding intravascular volume and increasing MAP, cardiac output and CBF, lowering ICP at the same time. Beneficial effects include improved systemic microcirculation through a reduction of red blood cell and endothelial cell oedema.[54] It also has an anti-inflammatory effect because it reduces leukocyte adhesion.[55,56]

The most common problem associated with the use of HTS, either in the form of repeated doses or in continuous infusion, is hyperchloremic acidosis. Other problems include ARF, arrhythmias, haemolysis, acute lung oedema and pontine myelinolysis. Pontine myelinolysis is usually observed with aggressive management of hyponatremia in malnourished individuals, alcoholics, and SIADH; it has not been described in the context of HTS-induced hypernatremia in normonatremic patients with ICH.[57] ARF is an infrequent complication with HTS, provided osmolality range and Na serum levels are respected.[18]

In 2002, Schimetta published a 9-year review on the safety and adverse reactions of hyperosmolar–hyperoncotic solutions (HHS) containing 7.2–7.5% HTS and 6–10% dextran in hypovolemic states. They found that there are approximately 5 adverse reactions for every 100,000 units of HHS used, that is, 8–16 reactions for every 100,000 patients treated with HHS. They showed a low potential of complications with the use of HHS in the clinical setting during almost one decade.[57,58]

The rebound phenomenon, seen also with mannitol, has a similar mechanism of action, but both the escape as well as the rebound phenomenon is less, due to the reflection coefficient. The reflection coefficient is the ability of the BBB of being impervious to a compound and its value range is 0–1 (zero coefficient = permeable, 1 = impermeable). The coefficient of mannitol is 0.9 and that of sodium chloride is =1. The best osmotic agents are those with a reflection coefficient close to 1.[16]

The complications of using HTS in neurocritical patients with TBI, subarachnoid haemorrhage and stroke in the neuro-ICU are shown in the study by Froelich et al. In 2010, they evaluated these potential complications with HTS and 0.9% saline solution in this patient population and, despite some weaknesses in their study, they propose the safety of continuous HTS treatment in neurological patients in the neuro-critical care unit. They tested their hypothesis that renal dysfunction, deep vein thrombosis and infection are not significantly different between patients treated with 3% HTS, CHS or 0.9% SS. They concluded that HTS therapy does not increase the incidence of infection or DVT rates. However, hypernatremia is closely linked to HTS infusions and renal dysfunction when sodium levels rise above 155 and 160 mEq/l.

Mannitol versus HTS

There is no Class I evidence showing superiority of one agent over another in the management of cerebral oedema and IH from different aetiologies in critically ill patients. In 2003, Vialet et al.[44] conducted a randomized prospective study to evaluate the clinical benefit of using HTS in refractory IH episodes. They compared 20% mannitol and 7.5% HTS in 20

patients with TBI and refractory IH (ICP = 25 mmHg). Although they found no difference in clinical outcomes, their study showed that, within its limitations, the administration of 2 ml/kg of HTS is an effective and safe treatment in IH episodes in the context of TBI. Francony et al. conducted a prospective clinical trial comparing equimolar doses of 20% mannitol with 7.45% HTS (255 mOsm; 230 and 100 ml, respectively) in stable patients with TBI or stroke and IH >20 mmHg. After 60 min of initiating the infusion, ICP dropped significantly (45% and 35%, respectively), without statistically significant differences in terms of the extent of the reduction in ICP between the two agents. A dose of 20% mannitol is as effective as 7.45% HTS in reducing ICP.[59]

In 2011, Scalfani et al. studied the effects of mannitol and HTS on cerebral blood flow in 8 patients with severe TBI. They used PET to measure CBF before and 1 h after the administration of equiosmolar quantities of 20% mannitol at 1 g/kg or 23.4% HTS at 0.686 ml/kg. They found that both agents are effective in lowering ICP and increasing CPP. They did not find significant differences between the two agents, but the sample size is very small to allow a definitive conclusion.[60]

Kamel,[61] in that same year, carried out a meta-analysis of all randomized trials comparing mannitol and HTS for the treatment of IH. Five well-designed trials were found, with 112 patients and 184 episodes of elevated ICP. They pointed out that the odds ratio for the control of intracranial hypertension was 1.16 in favour of HTS, with a mean reduction of ICP of 2.0 mmHg over mannitol; both results were statistically significant. The conclusion was that HTS may be more effective than mannitol for the treatment of ICP elevation, although the meta-analysis was limited by the small number and size of the eligible trials.

In 2009, The Neurocritical Care Society sent an online survey to its members in order to determine the usual management for the treatment of IH. They asked about the agent used most frequently, dose, and follow-up method. They received 295 responses, 279 of which were complete and 80% were from physicians.

The majority (54.9%) favoured the use of HTS, while 45.1% preferred mannitol. However, 95.4% of the respondents used mannitol in clinical practice, 83% used bolus doses, 80% used serum osmolality for follow-up, and only 22.5% used the osmolar gap for follow-up. The use of HTS in clinical practice was reported by 89%, mostly in the form of continuous infusion. Those who preferred HTS reported that it was easier to assess and had less systemic side effects, less rebound and ARF, and longer control of ICP. In contrast, those who preferred mannitol mentioned longer experience with the drug and ease of use because no central venous access is required.[62] It is clear that both agents are trusted by neuro-intensivists even though there is no agreement regarding dose, concentration or follow-up.

At present there is no pharmaco-economic analysis of mannitol and HTS solutions. The average purchase cost is approximately $12/100 g of mannitol versus $1.2/30 ml 23.4% saline solution. An equiosmolar dose is 0.686 ml/kg 23.4% saline solution versus 1 g/kg 20% mannitol.[63]

In 2012, Mortalazavi et al.[64] carried out a review and meta-analysis on the treatment of IH with HTS. The review included 36 articles, of which 10 were prospective randomized controlled, 1 non-randomized prospective, 15 observational prospective and 10 retrospective studies. Of the 36, 12 compared mannitol with HTS: 1 prospective non-randomized, 7 prospective randomized and 4 retrospective studies. Of these 12 studies, only 6 compared mannitol and HTS. Of the 12 comparative studies, those of De Vivo et al., [65] Francony et al.[59] and Larive et al.[66] did not find HTS to be superior to mannitol in terms of ICP or clinical outcomes. However, 9 comparative studies, 7 of which were randomized prospective controlled studies, showed that HTS was better at controlling ICP than mannitol. In 6 studies, greater ICP reduction was shown when adding HTS after mannitol administration. Two studies showed prolonged control of ICP, and 1 study showed that patients treated with HTS had less IH episodes per day than those who received mannitol.[64] In terms of clinical outcomes, the studies were not consistent: Ichai showed an improved GCS one year later in the HTS group; Yildizdas et al.[68] showed the best results with the lowest mortality rate and shorter time in coma, even though it was a retrospective study; in contrast, Vialet et al.[44] did not find differences in the 20 patients in the study, in terms of mortality rate or neurological outcomes at 90 days.

HTS administration, either as bolus or in infusion, has shown to be effective, although there are more studies with bolus administration than with infusion administration. In 11 studies, HTS infusion was used and the majority showed it to be effective for ICP control, but only 3 of those studies were prospective and randomized. Of those 3 studies, only 2 suggest infusion administration. In contrast, of the 26 studies in which HTS boluses were administered, 7 were prospective randomized studies, and 6 support bolus use. In 1999,[67] one study showed the worst mortality rate with the use of infusion, while no study using bolus doses showed these poor results.

Brain tumours

Cerebral oedema rarely presents in a pure form, and the two types of oedema are found together in many clinical situations, making clinical distinction difficult. Generally, intracerebral peritumoral oedema is vasogenic.

There are few studies comparing mannitol and HTS in the pure setting of cerebral relaxation in tumours. De Vivo et al. conducted a prospective randomized comparative study in supratentorial tumours. They randomized 30 patients into 3 groups with ASAI-II, a mean age of 58 years, and GCS of 15 on admission. One group received mannitol, the second group received Mannitol + HTS and the third group received only HTS starting at the time of skin incision, and continued with the treatment for 72 h, using boluses three times per day. They concluded that HTS is an effective alternative for lowering ICP in humans without reducing CVP or serum osmolality. It has a low probability of anaphylactic reactions or of transmitting infectious agents, and it easily controlled by serum Na levels. It is an effective alternative to mannitol in intracranial surgery.

In 2007, Rozet et al. published a prospective double-blind randomized study on the effect of equiosmolar solutions of mannitol versus HTS on intraoperative brain relaxation and

electrolyte balance. The study included 40 elective patients, the majority ASA-III, taken to surgery for supratentorial tumours, posterior fossa procedures, AVM and aneurisms, with and without subarachnoid haemorrhage. They divided them into two groups to receive 5 ml/kg of 20% mannitol ($n = 20$) or 5 ml/kg of 3% HTS ($n = 20$). They measured haemodynamic variables, fluid balance, blood gases, lactate and osmolality (blood, CSF and urine). The surgeon assessed brain relaxation according to four scores (1 = relaxed, 2 = satisfactory, 3 = firm, 4 = bulging). They found that there was no difference in brain relaxation, blood glucose, cerebral arteriovenous O_2 difference, or difference in lactate levels, between the two hyperosmolar agents. Despite the similarities between the two, the mannitol group showed a more profound diuretic effect ($p = 0.001$) and a higher negative fluid balance. They concluded that both mannitol and HTS increase CSF osmolality and are associated with equal levels of brain relaxation, arteriovenous O_2 difference and lactate during elective craniotomy. They recommend that HTS is a safe alternative to mannitol in brain size reduction in patients with and without subarachnoid haemorrhage, in particular if they are haemodynamically unstable.[69]

In 2011, Wu published a prospective randomized double blind study in 50 patients comparing the effect of 3% HTS versus 20% mannitol to assess brain relaxation in supratentorial tumour surgery, length of stay in the neuro-ICU and length of hospital stay. He concluded that brain relaxation with the use of 3% HTS was more satisfactory ($p = 0.01$) than with 20% mannitol in craniotomy for supratentorial tumour surgery. HTS led to a significant increase in serum sodium ($p < 0.001$) when compared with mannitol and there was greater diuresis in the mannitol group ($p < 0.001$). Hospital and neuro-ICU length of stay were similar in the two groups. Although the study grouped the patients for the majority of the characteristics measured, and although it is the largest study conducted in humans until 2011 in supratentorial tumours, it is worth nothing that it did not measure ICP routinely and it excluded patients with signs of IH. No mention is made of patient GCS or of the various parameters that may affect brain relaxation during surgery, such as preoperative radiological characteristics (tumour size, histology, peritumoral oedema, and midline deviation).[70]

Several studies have looked into the cerebral effects of mannitol and HTS in patients with normal ICP. Gemma et al.[71] reported that HTS and mannitol provide satisfactory cerebral relaxation in patients taken to elective craniotomy. This study was conducted with different neurosurgical procedures and non-equiosmolar doses of HTS and mannitol. The study by Vilas Boas et al. also assessed relaxation in 20 patients taken to different elective neurosurgical procedures, comparing the use of 20% mannitol with iso-oncotic HTS (7.2% HTS + 6% HES [200/0.5]). No statistically significant differences were found in terms of cerebral relaxation, hence the conclusion that single doses with equivalent osmolar load of either of these agents are effective and safe for general cerebral relaxation during elective neurosurgical procedures under general anaesthesia. Of 4 prospective randomized studies, 3 recommend HTS as a safe alternative to produce cerebral relaxation in patients with supratentorial tumours.[72]

Traumatic brain injury

Elevated ICP may occur in TBI in the presence of haematomas or cerebral oedema, and continues to be an important focus of patient care. Fluid resuscitation in patients with TBI is of critical importance because of the need to avoid hypotension and secondary neurological injury, which result in increased mortality in these patients. The Brain Trauma Foundation in its management guidelines for TBI is clear in stating that hypotension must be avoided because it is an isolated parameter of poor prognosis. Fluid resuscitation in this population, particularly with HTS alone or combined with dextran, restores intravascular volume with less volumes,[73] increases CPP, lowers ICP,[74] and modulates the inflammatory response.[75–82] Given all these benefits, neurological outcomes should improve at least in theory. This led Bulger et al.[77] to conduct a multi-centre randomized controlled study in 1282 patients comparing saline solution, HTS or HTS + dextran. They conclude that although they do not rule out the benefit of HTS, there was no benefit in terms of survival, and that there is apparently no strong reason to use HTS in TBI as part of the pre-hospital management.[78]

There are no firm recommendations as to which of the two agents should be used, but mannitol is used more frequently as first-line therapy for TBI-associated IH, followed by HTS as second-line therapy when there is no response to mannitol. Several authors report that both agents have a similar effect in equiosmolar doses,[59] and others show that HTS is more effective than mannitol in lowering ICP in TBI.[44,79] The goals of osmotherapy are to maintain CPP and lower ICP, but cerebral oxygen tissue tension ($PbtO_2$) is now emerging as an additional therapeutic target in the management of these patients. Observational studies have shown a relationship between $PbtO_2$ reduction and poor outcomes[80,81] and suggest that therapy targeted on maintaining $PbtO_2$ may improve clinical outcomes.[82] Little is known about the impact of HTS and mannitol on $PbtO_2$ in patients with severe IH from TBI and refractory IH. In 2009, Odd published a study on TBI with IH managed with mannitol, followed by HTS when control was not achieved. They studied $PbtO_2$ and concluded that in TBI with IH refractory to mannitol the administration of 7.5% HTS lowered ICP further, increased CPP, cardiac output and brain oxygenation, thus maintaining systemic and cerebral haemodynamics.[43] Rockswold examined the effects of 23.4% HTS on IH and $PbtO_2$ in patients with TBI that did not respond to sedation, hyperventilation and CSF drainage. They obtained ICP reduction and $PbtO_2$ increase.[83]

There are multiple studies that show that HTS – particularly 23.4% HTS – used in TBI with IH after the use of mannitol, led to greater and longer ICP reduction. Lazaridis, in a meta-analysis conducted in 2013, identified 11 papers on the use of 23.4% HTS to assess percentage reduction of ICP with a 95% CI of 55.6% at 60 min after the administration, with $p = <0.0001$. He concludes by stating that 23.4% HTS is a low-cost, small-volume solution which reduces ICP by 50%.[63]

In a meta-analysis of 36 articles carried out in 2012, Mortazavi found 16 on TBI, including 4 prospective randomized, 1 prospective non-randomized, 7 prospective observational, and 4 retrospective studies. In all 7 of the prospective studies,

a significant ICP reduction was found, with a mean reduction of 20–60%, and no evidence of rebound phenomenon. Of the 16 studies reviewed, including 4 prospective randomized studies and multiple observational studies, the data support the use of HTS as an effective means to lower ICP in patients with TBI. The 5 that compared HTS with mannitol showed a more significant lowering of ICP after HTS administration. Only 1 study out of the 36 articles reviewed found a better long-term result in patients treated with HTS, compared with mannitol.[64]

The only Cochrane meta-analysis on mannitol reports that the use of this agent for the treatment of elevated ICP may have a beneficial effect on mortality when compared to pentobarbital, but may have a negative effect on mortality when compared to hypertonic saline solution. No sufficient data were found on the effectiveness of pre-hospital use of mannitol.

Stroke

Infarction affecting the entire territory of the MCA occurs in 10–20% of patients with ischaemic stroke.[83,84] Patients with large hemispheric infarctions are at a high risk of intracranial pressure elevation because of cerebral oedema. Oedema following an ischaemic stroke begins within 1–3 days, peaks within 3–5 days, and lasts up to two weeks.[85,63]

There is little research about the use of hyperosmolar therapies in patients with ischaemic stroke, and there is no uniform approach to its use. Schwarz et al.[50] compared the effect of 100 ml and 75 ml of HTS, and of 60 g/l of HES and 200 ml of 20% mannitol in equiosmolar doses in 9 patients with 30 episodes of IH. Therapy with hyperosmolar agents was used in an alternating fashion and IH was considered to be present with an ICP >25 mmHg or pupillary abnormality. Management success was defined as a 10% reduction in ICP, and this happened in 10 out of 14 patients treated with mannitol and in 16 patients treated with HS/HES. They conclude that single doses of 100 ml HS-HES or 40 g of mannitol are effective at lowering elevated ICP in patients with cerebral oedema and show no negative effects on MAP or CPP, although HS-HES appear to be faster and more effective at lowering elevated ICP. Moreover, there is the advantage of being able to use HS-HES successfully again after mannitol has failed. In 2002, Schwarz confirmed these data in a prospective study with 8 stroke patients and 22 episodes of IH, which had not responded to conventional management using 200 ml of 20% mannitol. They administered 75 cc of 10% HTS for 15 min and observed a reduction of IH in the 22 episodes, with improvement of PPC which was still maintained up to 4 h later.[51] Although it is known that osmotherapy with these two agents is effective, little is known about the effect of HTS on healthy and injured neurons in the brain. The first study reporting on the response of healthy neurons, and neurons injured in vitro with glutamate in a hypertonic and hyperoncotic environment, was conducted by Himmelseher in 2001. This study in rats showed that, after 24 h, the viability of healthy hippocampal neurons exposed to HTS was reduced by 30% ($p < 0.05$), and injuries induced by glutamate were not exacerbated, which indicates that the mortality of injured neurons was not increased by HTS. Although it is not appropriate to extrapolate data obtained in a cell culture models to clinical situations, these data show that HTS may potentially damage hippocampal neurons in vitro.[86] Another consideration in stroke patients is post-ischaemia cerebral oedema, which increases ICP, contributing to secondary injury and brain herniation, and increasing morbidity and mortality in these patients. Toung et al. conducted a prospective study in rats and showed the presence of significant cerebral oedema after stroke in both hemispheres (the injured as well as the contralateral hemisphere), but with a different progression. Mannitol therapy was more effective at reducing water in the ischaemic hemisphere of the brain, but HTS was equally effective at dehydrating both hemispheres of the brain (ischaemic and non-ischaemic).[87] The question to be solved is when to start hyperosmolar therapy in stroke, considering that different studies have shown mixed results. In a study in rodents in 2000, Bhardwaj et al.[88] showed that the volume of the lesion worsened with HTS when it was administered at the time of focal ischaemia reperfusion. Two years later, Toung et al. showed that the volume diminished when therapy was initiated 24 h after the focal ischaemia and serum NA^+ was maintained between 145 and 155 mEq/l.[87] Finally, another question is how do osmotic agents work in reducing ICP in these patients. Several theories have been proposed. One theory is that they reduce water content in the brain, and a second theory is that they reduce viscosity and cerebrovascular resistance, giving rise to compensatory vasoconstriction and reduced CBV. In 2011, Diginger et al. compared 20% mannitol versus 23.4% HTS in 9 patients severely affected by cerebral oedema secondary to brain ischaemia with a midline deviation >2 mm. They measured CBF, CBV and $CMRO_2$ in an attempt at understanding the mechanism of action of osmotic agents. They found varying degrees of increased CBF in the contralateral hemisphere of patients with ischaemic stroke after osmotic therapy, apparently mediated by blood pressure. They did not find evidence to support the theory that osmotic agents reduce CBV, arguing against the theory that they reduce ICP by creating cerebral vasoconstriction[89] The AHA guidelines still in force show that osmotherapy is among other aggressive medical measures for the treatment of critically ill patients with malignant cerebral oedema after a large cerebral infarction. However these measures have not been tested and, consequently, they are not recommended (Class IIa, level C evidence).[90]

Subarachnoid haemorrhage (SAH)

Cerebral blood flow drops globally after SAH and this is manifested in worsening of the neurological status. The worse the patient's neurological status, the lower CBF will be.[91] In 2003, Tseng submitted an interesting report on HTS effects on CBF in areas of poor cerebral perfusion in patients with high grade SAH. They administered 23.5% HTS to 10 patients with high grade SAH and measured CBF, ICP and CPP. HTS resulted in an important drop in ICP, which persisted for more than 200 min, and in a significant increase in MAP, leading to an increase in CPP. He determined that 23.5% HTS increases CBF in patients with high grade SAH, and that this effect is associated with improved blood rheological indices.[92] Al-Rawi et al.[93] showed

that the increase in CBF is accompanied by improved tissue oxygenation and metabolism when patients are treated with 23.5% HTS and saline solution and monitored for cerebral metabolic rate of oxygen and microdialysis probes. In 2010, the same group showed, in 44 patients with high grade SAH, that HTS increases CBF and improves cerebral oxygenation significantly during 4 h after the infusion. This favourable result is associated with improved cerebral tissue oxygenation for more than 210 min.[94] In a review study in 2012, Mortalazavi et al.[64] found 11 studies in patients with non-traumatic brain injury and SAH. Of the 11 studies, two[46,95] used HTS during IH peaks and increased CBF was found in 5 studies[92,93,96] in patients with high grade SAH. The study by Bentsen et al.[95] compared bolus therapy with HTS/HES with saline solution for the control of ICP in patients with SAH and found enhanced reduction during the 210 min of the study. In 6 studies there was a significant reduction of ICP from the start, and the maximum reduction went from 38% to 93% over an average period of time of 30–60 min after the infusion. No ICP rebound effect was observed in any of the trials during their respective study periods.

Intracerebral haemorrhage (ICH)

Intracranial hypertension occurs during the acute phase of ICH and it is a predictor of poor prognosis in these patients. There is no clear knowledge to date of which are the best modalities for the management of this condition. One of the first reports on the use of HTS in ICH was published by Qureshi in 1998, involving two patients with non-traumatic ICH in whom he infused HTS and observed clinical improvement 24 h after the infusion. Still under the continuous HTS infusion, 48–96 h after the episode, the brain CT scan of both patients revealed extension of the cerebral oedema, suggesting a rebound effect similar to that already described with mannitol.[97] One year later, Qureshi conducted experimental studies in dogs, comparing the effects of equiosmolar doses of 20% mannitol, 3% HTS and 23.4% HTS. After inducing haematomas, they measured ICP, cerebral perfusion pressure, cerebral oxygen extraction and oxygen consumption, as well as CBF in regions close to the haematoma and distant to it. All of the measurements were recorded at the beginning of the study, before treatment, and 15, 30, 60, and 120 min after treatment. They observed reversal of transtentorial herniation and restoration of CBF and $CMRO_2$. ICP dropped in all treatment groups after 2 h, but only in the animals that received continuous infusion of 3% HTS. They also showed increased CPP and a lower volume of hemispheric water compared to the animals that received 23.4% or mannitol. Both 3% and 23.4% hypertonic saline solution was as effective as mannitol in the treatment of intracranial hypertension observed in ICH.[98] HTS may have a longer duration of action, especially when used in a 3% solution. None of the three treatment regimens influenced cerebral blood flow or brain metabolism.[7]

In 2007, Tseng showed that HTS administration may revert cerebral ischaemia to normal perfusion in patients with poor grade SAH. After 30 min of the administration of 2 ml/kg of 23.5% HTS in a patient with SAH, there was a 10.3% increase in MAP, CPP also increased by 21.2% ($p < 0.01$), and the ICP dropped by 93.1% ($p < 0.01$) after 1 h. These changes persisted for a period of 80–180 min.[99]

Conclusions

It has been very difficult to assess the efficacy of hypertonic saline solution or compare it with other protocols used for mannitol due to the wide variety of concentrations available and the number of protocols employed.

Both mannitol and HTS have proven to be effective at controlling ICP, through different mechanisms; osmotic dehydration of the cerebral interstitium; reduction of blood viscosity; increased red blood cell deformation; and improved microcirculation.

The use of mannitol and hypertonic saline solution in neurocritical patients varies considerably among centres and there is no consensus regarding which of the two is the agent of choice. The majority of the data reviewed suggest that HTS offers more favourable results in the control of ICP and all types of IH, regardless of concentration. Some authors suggest that 3% HTS and 23.4% HTS show more beneficial effects in tumours and TBI, respectively, than mannitol. A meta-analysis found 8 prospective randomized studies with a high failure rate of mannitol-based therapy. It is still to be determined whether HTS should be administered in the form of a drip or infusion; both are effective but there are more results, and none of them worse, with the use of bolus doses. HTS produces less osmotic diuresis, thus maintaining more stable systemic and cerebral haemodynamics in the neurocritical patient, considering that it does not only lower ICP and maintain CPP, but it also increases $PtbO_2$.

The benefit of HTS relative to long-term neurological outcomes compared to that of mannitol is yet unclear. A large prospective randomized study is needed in order to answer this question. Many of the problems have not been elucidated yet, hence the need for additional research in order to arrive at a definitive conclusion about the superiority of these hyperosmolar agents and for protocols with adequate doses and concentrations of these agents as first-line therapy to control intracranial hypertension.

Conflict of interest

The authors have no conflicts of interest to declare.

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