

Mannitol or hypertonic saline for intracranial hypertension?

A point of view

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Osmotically active solutions have been used for more than 30 years in the treatment of intracranial hypertension. The traditional agent of choice has been mannitol, but hypertonic saline has recently emerged as an alternative. Here, we discuss the systemic and cerebral effects of these two substances, as well as their side effects and complications, and make recommendations about their clinical use.

Mannitol

Mannitol has been the agent of choice in osmotherapy for cerebral injury since the 1960s. It is a mannose-derived simple alcohol, which is easy to prepare and use, stable in solution, inert, not metabolised, freely filtered by the kidneys without being reabsorbed, and low in toxicity. Its distribution volume corresponds to the extracellular compartment.¹⁻⁷ The effects of mannitol on the central nervous system have been well described, but the mechanisms are still not completely understood.

Rapid administration of a 15%–20% mannitol solution produces similarly rapid effects, reaching maximum intensity after 30–45 minutes, and returning to baseline after 2–12 hours.⁸ Osmolarity is increased by 15–25 mOsm/L.⁹⁻¹¹ The blood–brain barrier reflection coefficient is about 0.9.¹²⁻¹⁶ (Box 1). The systemic and cerebral effects are due to circulatory, diuretic and rheological mechanisms.

Circulatory effects

An acute infusion of 15%–20% mannitol solution induces an increase in cardiac output and filling pressures, and a sharp but temporary increase in arterial pressure and cerebral perfusion pressure.¹⁷ Cardiac output rises up to about 30%, increasing cerebral blood flow. Several studies show that mannitol strongly affects systemic vascular resistance because of its rheological effects. This increases oxygen transport at systemic and cerebral levels.⁹

Diuretic effects

The osmolarity of a 15% mannitol solution is 1200 mOsm/L. Mannitol is not metabolised and is excreted unaltered by the kidneys. For each mannitol molecule, five water molecules are excreted. Its diuretic effect occurs about 30–45 minutes after intravenous infusion.

Rheological or microcirculatory effects

Mannitol is a free radical scavenger and has particularly strong microcirculatory effects, increasing capillary blood

ABSTRACT

Osmotically active solutions, particularly mannitol, have been used for more than 30 years in the treatment of intracranial hypertension. Recently hypertonic saline has emerged as an alternative to mannitol. Both solutions are used worldwide, and their indications and long-term side effects are well known. More recently, knowledge about their effects has increased, both limiting and expanding their clinical use. Here, we compare the systemic and cerebral effects of mannitol and hypertonic saline, as well as their side effects and complications. Finally, we make recommendations about their clinical use.

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flow. These effects have been described for the cerebral circulation, and are transient and based on a rise in capillary volaemia, a feature which distinguishes mannitol from other osmotically active molecules, such as urea and glycerol, that are no longer used clinically.^{8,18,19}

Effects on intracranial pressure

Mannitol reduced intracranial pressure. Nevertheless, its dual and paradoxical effects are also well known, especially in the presence of significant damage to the blood–brain barrier. In this context, there is an extremely high risk of producing a paradoxical “reverse” osmotic gradient, which will then lead to delayed increases in intracranial pressure as described below.²⁰⁻²² In one clinical study, mannitol generated only a 25% initial decrease in intracranial pressure.²³ Clinical and experimental studies show that, after injecting a 15% mannitol solution, intracranial pressure decreases by about 5 mmHg.^{17,24-26} In humans, cerebral perfusion pressure generally improves after mannitol infusion.²⁷ High levels of osmolarity and natraemia attenuate these effects.²⁸ Water is extracted from areas of both ischaemic and healthy tissue.^{29,30}

However, clinical reports indicate that consecutive and repeated doses of mannitol in the setting of blood–brain barrier disruption may cause reverse osmotic gradients and even increases in intracranial pressure, the so-called paradoxical reverse osmotic gradient.^{29,30} Furthermore, in some clinical situations, particularly in the presence of midline

Table 1. Osmolarity, blood–brain barrier reflection coefficient (C-reflection) and typical dose of hypertonic solutions

Solution	Osmolarity (mOsm/L)	C-reflection	Typical dose
Mannitol			
15%	1150	0.9	0.5–2 g/kg
20%	1400	0.9	0.25–2 g/kg
Saline			
3.5%	1195	1.0	1.4 mL/kg
7.5%	2560	1.0	1.2 mL/kg
10%	3410	1.0	0.9 mL/kg
24%	8008	1.0	0.7 mL/kg

deviation, the uncontrolled use of mannitol may worsen deviation because of rises in transhemispheric pressure gradients. These are secondary to reductions in intracranial pressure that are greater in the healthy hemisphere than in the abnormal areas. This phenomenon been observed particularly in focal diseases,² and occurs in the absence of changes in average intracranial pressure.^{1,31}

Clinical uses

Mannitol is used to manage intracranial hypertension with preserved autoregulation and hypoperfusion flow patterns.³ It is also used to manage neurosurgical emergencies with an intracerebral mass amenable to evacuation, where surgery is planned within a brief period.^{31,32}

Hypertonic saline solutions

Hypertonic saline solutions with increasing concentrations were re-incorporated into patient care over 20 years ago, especially for resuscitation of patients with severe trauma and haemorrhagic shock.^{16,33,34}

In the clinical and experimental setting, these solutions increase plasma osmolarity, with an effect comparable to that of mannitol, causing a reduction in cerebral water content secondary to a sharp increase in plasma sodium, an effect which persists for at least 18 to 24 hours.^{8,18,35-37} This is due to the fact that adequate levels of intracerebral water and circulatory stability are regulated and maintained in both the injured and uninjured hemispheres.^{4,36}

Circulatory effects

With use of hypertonic saline solutions at progressively increasing concentrations (3%, 5%, 7.5%, 10% and 23.5%), the osmolar load also rises gradually, whereas the volume required decreases. Systemic effects are

marked by a sharp increase in systemic arterial and venous filling pressures, right and left ventricular end-diastolic pressure and cardiac output. There is also a rapid rise in effective plasma volume and cerebral blood flow.³⁸ Similarly, if plasma osmolarity is below 300 mOsm/kg, high osmotic gradients are generated between plasma and the interstitium, inducing systemic and cerebral water extraction. The volume extracted is directly proportional to the osmotic gradient generated. After use of these substances, significant degrees of natriuresis and polyuria are frequently observed,³⁹ which may also further induce hyperosmolarity in patients with intracranial hypertension.

Effects on intracranial pressure

The clinical effectiveness of these hyperosmotic solutions in reducing intracranial pressure has been known for many years. However, the mechanisms responsible remain unclear and controversial.

The first hypothesis is that these substances reduce the volumes of cerebral astroglial cells through increased activity of type 4 aquaporin water channels. However, a systematic search of the literature showed that this mechanism is quantitatively insignificant. Published data are contradictory, particularly in the case of focal injuries, and in regard to the relative effects of these solutions in both normal and injured areas.^{4,17,18}

Another hypothesis is based on the view that a sharp increase in circulating volume increases systemic arterial pressure. If cerebral autoregulation is preserved, this increase causes cerebral vasoconstriction while reducing cerebral blood volume and, therefore, decreases intracranial pressure.^{5,40}

The third hypothesis is that cerebral blood volume is decreased because of improvements in brain rheological status, which favour vasoconstriction. This implies a decrease in intracranial pressure only if resistance and flow autoregulation is maintained.¹⁸

The final hypothesis states that the osmotic effects of hypertonic saline reduce the supra- and infratentorial cerebrospinal liquid volume. Consequently, intracranial pressure decreases.⁴¹

Effects on electrolyte balance

Hypertonic saline induces a progressive increase in natraemia and osmolarity. However, severe hypernatraemic–hyperosmolar states have been reported only when these solutions have been used repeatedly, with sodium levels > 160 mmol/L. Hypovolaemia and excessive use of hyperosmotic solutions favour hypernatraemic states, and exponentially increase secondary effects.^{12,38}

Clinical uses

Hypertonic saline can be used for refractory intracranial hypertension as second-line therapy. In these cases, intracranial pressure significantly decreases, and cerebral perfusion pressure improves, with better and longer-lasting control even when static and dynamic autoregulation is abolished.⁴² Hypertonic saline can also be used as first-line therapy to manage intracranial hypertension in patients with severe cerebral trauma with hypovolaemia, cerebral hyperperfusion flow patterns and midline deviation. Although this therapy has not been shown to alter patient outcomes in randomised controlled trials, we have clinical experience of its effectiveness as initial treatment in these patients, as well as evidence from computed tomography and magnetic nuclear resonance imaging that it does not cause the increments in midline deviation seen with mannitol.⁴⁰ Hypertonic saline can also be used as fluid resuscitation in patients with multitrauma and traumatic brain injury,⁴³ and to treat secondary intracranial hypertension in patients with trauma or stroke presenting with hyponatraemia (< 135 mmol/L).⁴⁴

Controlling intracranial pressure with midline shift

It has been known for many years that 15% and 20% mannitol solutions, as well as hyperosmotic solutions at increasing concentrations (3%, 5%, 7.5%, 10% and 23.5%) strongly affect brain-water regulation. Equimolar doses of mannitol and hyperosmotic solutions have equivalent effects on intracranial pressure when autoregulation is preserved. The only difference is the intense osmotic diuresis induced by mannitol, and the eventual hypernatraemia that occurs with repeated use of saline solutions. However, hypertonic saline solutions are more effective in patients with midline shift without removable masses.³⁸ The reason is that, although water is extracted from both hemispheres, this extraction occurs in a parallel manner and maintains the transhemispheric water gradient. Reverse osmotic gradients, such as those seen with mannitol, have not been reported for hyperosmotic saline solutions, nor has rebound intracranial hypertension.

Regarding the above conceptual framework, we propose that hypertonic solutions would be more cost effective than mannitol as first-line therapy in patients with intracranial hypertension whose autoregulation is maintained or altered secondary to cerebral trauma. In this setting, repeated use of mannitol should be avoided because of the high risk of generating reverse osmotic gradients, rebound intracranial hypertension and increased diuresis.

For patients with cerebral trauma and intracranial hypertension who have lost autoregulation, as well as those in whom increases in intracranial pressure are refractory to the

use of mannitol, we also suggest that hypertonic saline solutions may be effective.

For patients with cerebral trauma or stroke and midline deviations < 10 mm, with no removable intracerebral mass, the use of hypertonic saline solutions is also recommended, as seemingly more cost-effective and safer.⁴⁵ This treatment should reduce the risk of increasing transhemispheric pressure gradients, and have an equivalent or superior effect to mannitol in reducing global intracranial pressure.^{25,26,44,45}

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