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Review Article

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Optimizing Mannitol Use in Managing Increased Intracranial Pressure: A Comprehensive Review of Recent Research and Clinical Experiences

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ABSTRACT

Mannitol, derived from mannose sugar, is crucial in treating patients with elevated intracranial pressure (ICP). Its dehydrating properties at the cellular and tissue levels increase plasma osmotic pressure, which is studied for its potential to reduce ICP through osmotic diuresis. While clinical guidelines support mannitol use in these cases, the best approach for its application continues to be debated. Important aspects needing further investigation include: 1) bolus administration versus continuous infusion, 2) ICP-based dosing versus scheduled bolus, 3) identifying the optimal infusion rate, 4) determining the appropriate dosage, 5) establishing fluid replacement plans for urinary loss, and 6) selecting monitoring techniques and thresholds to assess effectiveness and ensure safety. Due to the lack of adequate high-quality prospective research data, a comprehensive review of recent studies and clinical trials is crucial. This assessment aims to bridge the knowledge gap, improve understanding of effective mannitol use in elevated ICP patients, and provide insights for future research. In conclusion, this review aspires to contribute to the ongoing discourse on mannitol application. By integrating the latest findings, this review will offer valuable insights into the function of mannitol in decreasing ICP, thereby informing better therapeutic approaches and enhancing patient outcomes.

Keywords: Mannitol; Osmolar concentration; Intracranial pressure; Hypertonic solutions

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Conflict of Interest
The authors have no financial conflicts of interest.

INTRODUCTION

Mannitol, a sugar alcohol derived from mannose sugar, functions to dehydrate cells and tissues by elevating plasma osmotic pressure. Its osmotic diuresis property has been utilized in numerous studies to decrease intracranial pressure (ICP) in patients with cerebral injury. Although guidelines advocate for mannitol administration in such cases, the ideal usage remains a subject of debate. Key considerations include: 1) Bolus administration versus continuous infusion, 2) ICP-guided dosing versus routine scheduled bolus, 3) Optimal infusion rate, 4) Optimal dosage, 5) Fluid replacement strategies for urinary loss, and 6) Monitoring techniques and thresholds for mannitol: Selecting the optimal methods for assessing mannitol's impact and setting safe, efficacious thresholds.

Given the scarcity of high-quality prospective research data addressing these concerns, it is crucial to examine recent investigations and clinical case studies to enhance our understanding of mannitol's optimal application in patients with cerebral injuries.

PROPERTIES OF MANNITOL

Mannitol is a water-soluble sugar alcohol with the molecular formula $C_6H_8(OH)_6$ (**FIGURE 1**).[3] It is freely filtered through the glomerulus but not reabsorbed in the urinary tubules, leading to a difference in osmotic concentration between the tubules and microvessels, which can induce osmotic diuresis. Mannitol is a one of the well-known osmotic diuretics. Although mannitol itself is acidic (pH 6.3), the addition of sodium bicarbonate in medical formulations adjusts the pH.

Pharmacokinetics of mannitol

Absorption

Mannitol, a potent water-soluble compound containing 6 hydroxyl groups (OH), exhibits poor intestinal absorption, making it unsuitable for oral administration and primarily administered intravenously. Oral administration may lead to osmotic diarrhea. The reduction in ICP commences 15–30 minutes after administration, with an action time of approximately 1.5–6 hours, and diuresis initiating after 0.5–3 hours.[20,42]

Distribution

Mannitol remains confined to the extracellular fluid (ECF) compartment and exhibits limited penetration of the blood-brain barrier (BBB) (osmotic reflection coefficient: 0.9). It is freely filtered through the glomerulus and neither reabsorbed nor secreted by the kidneys.

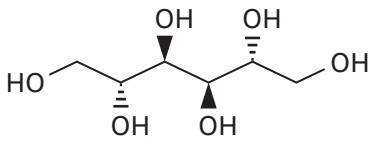

FIGURE 1. Chemical structure of mannitol.
This figure illustrates the molecular structure of mannitol, a sugar alcohol derived from mannose sugar. The structure consists of 6 carbon atoms, each bound to OH, forming a linear polyol with a characteristic chair conformation. The molecular formula for mannitol is C6H14O6. As a crucial osmotic agent, mannitol is commonly used in neurosurgical practice to reduce intracranial pressure, showcasing its importance in clinical settings. OH: hydroxyl groups.

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Osmotic reflection coefficient: This coefficient is a numerical value denoting a compound's relative impermeability to cross the BBB. A value of 0 signifies 100% BBB penetration, while a value of 1 indicates impermeability. Mannitol has an osmotic reflection coefficient of 0.9, while hypertonic saline (HTS) has a value of 1. As HTS does not pass through the BBB, there is no rebound effect even after prolonged administration, allowing for immediate cessation. However, with mannitol, long-term administration may result in partial BBB penetration and accumulation in brain parenchyma, necessitating a gradual reduction strategy to prevent rebound effects (taper-out withdrawal).

Metabolism

Mannitol can be minimally converted into glycogen in the liver and is primarily metabolized to fructose-6-phosphate. One advantage of mannitol over HTS is its ability to shift anaerobic glycolysis to aerobic glycolysis by acting on the glycolytic pathway (**FIGURE 2**).[20]

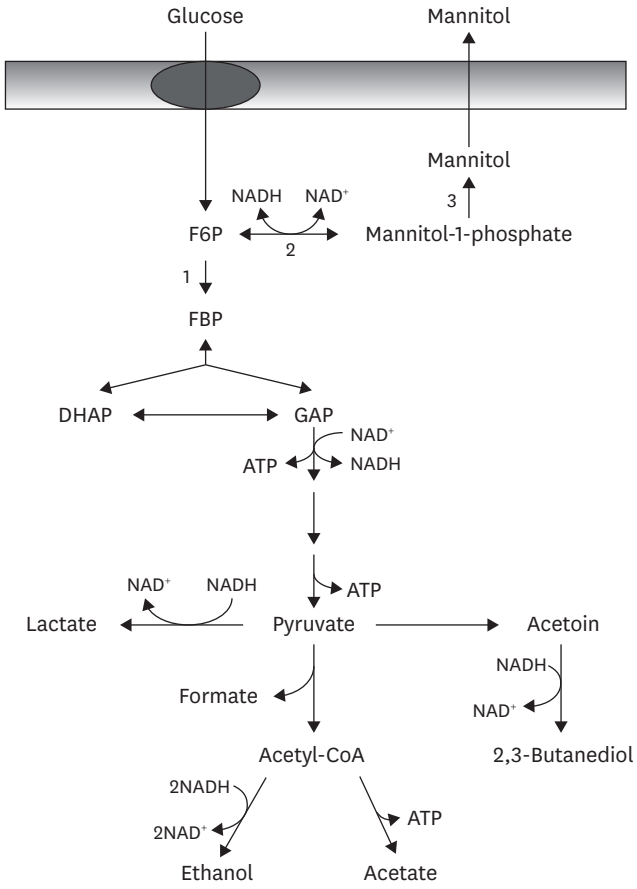

FIGURE 2. Mannitol metabolism and its influence on the glycolytic pathway.
This figure presents an overview of the metabolic pathway of mannitol and its interaction with the glycolytic pathway. Mannitol is primarily metabolized in the liver by the enzyme mannitol dehydrogenase, converting it to fructose. The fructose can then enter the glycolytic pathway through phosphorylation by fructokinase, yielding fructose-1-phosphate, which is subsequently cleaved by aldolase B to produce DHAP and glyceraldehyde. Both DHAP and glyceraldehyde can be further metabolized through the glycolytic pathway, ultimately generating energy in the form of ATP. This figure highlights the interplay between mannitol metabolism and the glycolytic pathway, demonstrating the broader metabolic implications of mannitol administration in neurosurgical applications.
DHAP: dihydroxyacetone phosphate, FBP: fructose 1,6-bisphosphate, GAP: glyceraldehyde 3-phosphate, NAD: nicotinamide adenine dinucleotide, NADH: nicotinamide adenine dinucleotide hydride, ATP: adenosine triphosphate, CoA: co-enzyme A.

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Excretion

Upon intravenous administration of mannitol, about 80% is excreted through the kidneys as an unchanged drug. Mannitol clearance is almost equivalent to the glomerular filtration rate (GFR). The half-life of mannitol typically ranges from 0.5 to 2.5 hours in individuals with normal renal function, while it varies from 6 to 48 hours in patients with renal failure.

Pharmacodynamics of mannitol

During the initial phase of mannitol administration, blood osmotic pressure increases due to elevated mannitol levels in the blood, causing water from interstitial tissue to shift into blood vessels and temporarily increasing plasma volume. Patients with heart failure should be monitored for pulmonary edema as plasma volume increases. Additionally, mannitol helps reduce intracranial or intraocular pressure by facilitating water movement into brain parenchyma blood vessels.

Mannitol is a low molecular weight (182.17 g/mol) compound that freely filters through the glomerulus without being reabsorbed. As mannitol passes through the glomerulus, it raises the osmotic pressure in the tubules, inducing osmotic diuresis. Approximately 80% of mannitol is filtered in the glomeruli as an unchanged substance and excreted in urine. This process inhibits water reabsorption in the tubules. In acute oliguria patients, administering mannitol can prevent renal dysfunction by increasing urine volume and can induce increased and normalized urine output even when GFR decreases due to severe fluid loss.

Following mannitol administration, sodium concentration in the body can change in various ways (hypernatremia vs. hyponatremia). In the early stages of mannitol use, urinary Na^+ excretion increases due to enhanced urine flow, and plasma volume expands as water transport into the blood increases, potentially causing hyponatremia. However, with long-term mannitol administration, free water loss surpasses Na^+ loss, resulting in hypernatremia.

In cases of high-dose mannitol administration or patients with renal failure, mannitol is not adequately eliminated from the body, leading to increased blood osmotic pressure and continuous water movement into the blood, ultimately causing hyponatremia.

Mechanism of action of mannitol

Osmotic gradient effect

Mannitol generates an osmotic pressure difference across the BBB, driving the movement of water from the brain tissue into the bloodstream. This leads to brain dehydration and a subsequent reduction in ICP. Generally, the osmolality of brain tissue is slightly higher than that of serum, with a blood-brain osmotic gradient across the BBB of about 3 mOsm/kg. However, mannitol administration significantly increases serum osmolality, reversing the osmotic gradient and causing water in the brain parenchyma to shift into blood vessels, thereby decreasing cerebral edema.

Reduced blood viscosity

Mannitol also helps regulate ICP by reducing blood viscosity. Four main factors maintain blood viscosity: plasma viscosity, hematocrit, red blood cell aggregation, and red blood cell deformability. Mannitol lowers ICP through various mechanisms, including a decrease in blood viscosity. It has been shown to reduce blood viscosity by lowering hematocrit, mean corpuscular volume (MCV), and enhancing red blood cell deformability.[4] In addition, studies have demonstrated the effectiveness of mannitol in reducing blood viscosity in animal models such as cats.[34]

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Cerebral vasoconstriction

Mannitol can induce vasoconstriction in the cerebral blood vessels, reducing blood volume in the brain and further decreasing ICP.[34]

ADMINISTRATION METHOD OF MANNITOL

Bolus versus continuous infusion

No studies directly compare intermittent (bolus dosing) and continuous infusion administration methods of mannitol, and there is insufficient evidence to determine the superiority of either approach. The primary mechanism mannitol reduces ICP is through its rheological effects, which involve decreasing water in the brain parenchyma via the osmotic gradient across the BBB and increasing blood viscosity. Mannitol's effect is optimized before the BBB structurally begins to leak into the brain parenchyma.

Intermittent (bolus dosing) use of mannitol induces autoregulatory vasoconstriction of cerebral arterioles by suddenly increasing cerebral blood flow, effectively reducing cerebral blood volume and ICP.[33] Given this mechanism of action, bolus dosing is advantageous over continuous infusion for rapidly establishing an osmotic gradient between the brain and plasma, maximizing water transport from the brain parenchyma, and eliciting a cerebral vasoconstriction response. Furthermore, mannitol has an osmotic reflection coefficient of 0.9, meaning some of it may accumulate in the brain parenchyma, especially in pathological conditions where the BBB is compromised.[27] Additionally, when neuronal cells are continually exposed to a hypertonic environment, they undergo neuronal shrinkage and then compensate by increasing intracellular osmole concentrations to return to their normal size.[1,31] Continuous infusion is not preferred because such a reaction gradually reduces mannitol's effectiveness and may lead to rebound swelling.

Collectively, the continuous infusion method was used to maintain the osmotic gradient consistently, focusing on the osmotic effect. However, many studies have suggested that bolus dosing of mannitol more effectively reduces ICP with fewer complications.[22,25,30,32,45,50] Consequently, bolus dosing is the preferred method.[23]

Rate of infusion

Numerous animal and clinical studies have demonstrated that rapid administration of mannitol can cause hypotension due to a sudden decrease in peripheral vascular resistance and hypovolemia.[9,15,39,41] Sudden hypotension was observed when the administration rate exceeded 0.1 g/kg/min (1.0 g/kg over 10 minutes), but hypotension did not occur when the administration was conducted over 15 to 30 minutes. In cases of hypotension, mannitol administration was halted, and blood pressure normalized within 2 minutes, though the increase in heart rate only normalized after 30 minutes.[39] Therefore, the administration rate should be regulated to ensure it does not exceed 0.1 g/kg/min (1.0 g/kg over 10 minutes).

Dosing

Although mannitol has been used very frequently in neurocritical care, the optimal dosage remains undetermined. This is due to the lack of class I-level evidence in numerous studies examining the relationship between mannitol dosage, ICP, cerebral perfusion pressure (CPP), and clinical outcomes. Furthermore, each study's target patient group with elevated ICP varies, resulting in controversies in research findings.

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A meta-analysis conducted by Sorani and Manley[44] revealed a weak linear correlation between mannitol dosage and changes in ICP. However, there was a strong association between the initial ICP level during mannitol administration and the degree of ICP reduction. In other words, the impact of mannitol dosage on ICP reduction was insignificant below a specific level (<20 mmHg), but the effect was evident above a 20 mmHg.

In Marshall et al.'s study,[30] even a low dose of 0.25 g/kg demonstrated effective ICP reduction, comparable to the 0.5 g/kg and 1.0 g/kg groups. Conversely, McGraw et al.'s research[31] showed a correlation between mannitol dosage and ICP reduction. Administering 10g of mannitol resulted in decreased ICP in only 50% of patients, but over 80% of patients experienced decreased ICP when 50 g was administered. Three randomized prospective clinical studies conducted by Cruz et al.[1042] investigated the relationship between mannitol dosage and clinical outcomes. In comatose patients due to acute subdural hematoma, high-dose (1.2–1.4g/kg) administration led to improvements in preoperative abnormal pupillary dilation and GOS at six months compared to the conventional dose (0.6–0.7 g/kg) group.[10] Similar results were obtained in a clinical study of patients with temporal lobe hemorrhage with abnormal pupillary dilation.[11] In comatose head trauma patients with bilateral pupillary dilation, early improvements in pupillary dilation and good GOS at six months were observed in the high-dose (1.4 g/kg) group compared to the conventional dose (0.7 g/kg) group.[12]

In summary, high-dose mannitol (≥1.0 g/kg, at least) generally had a more dose-dependent effect on reducing ICP and a longer duration than low-dose mannitol, although the difference in pressure reduction was not substantial. Low-dose mannitol was ineffective in reducing ICP in some patients.

Intoxication

The most concerning complications of mannitol administration include acute kidney injury (AKI) and electrolyte disturbances. Specifically, the risk of AKI is closely associated with the upper limit of mannitol dosage. While mannitol was once thought to prevent postoperative AKI by increasing renal blood flow, several subsequent studies reported that AKI occurs when mannitol administration exceeds the urinary excretion rate. Animal experiments and histological examinations revealed acute tubular necrosis and swelling in proximal renal tubules when high doses of mannitol (1.8–2.1 g/kg) were continuously used.

Dorman et al.[16] reported 8 patients with mannitol-induced AKI and found a relationship between the osmolar gap (OG), which indirectly reflects blood mannitol concentration, and AKI. A blood concentration of mannitol below 1,000 mg/dL decreases renal microvascular resistance and increases renal blood flow, but a blood concentration of 1000 mg/dl or more causes renal microvessel contraction, resulting in ischemic renal injury. The OG was greater than 55 in all patients with renal impairment except for one patient, corresponding to 1,000 mg/dL.

High-quality evidence on the optimal mannitol dose is lacking, but low doses (<0.5 g/kg) present issues with low efficacy and durability, while high doses (>1.5 g/kg) can lead to complications such as nephrotoxicity. As a result, a dose of 0.5–1.5 g/kg is recommended. However, in cases of emergent neuro-resuscitation due to ICP crisis, temporarily using a high dose of ≥1.5 g/kg is advised. In situations where an increase in ICP is suspected, the dose can be adjusted by repeatedly administering 0.25–1.5 g/kg while monitoring ICP as much as possible and observing the ICP reduction response after administering mannitol.

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Dose and special consideration

Mannitol and HTS combination

In certain situations, both mannitol and HTS are administered. This may occur in cases of refractory increased ICP that does not respond to mannitol or when the use of the mannitol should be adjusted based on blood test results. The efficacy and safety of combined administration of mannitol and HTS are not well established. The most concerning complication is AKI, and both mannitol and HTS can induce AKI through different mechanisms. Narayan et al.[35] reported that combined treatment with mannitol and HTS did not increase the risk of renal injury compared to HTS alone in patients with traumatic brain injury. However, there is still insufficient evidence regarding the efficacy or safety of the combined use of these two agents, so caution should be considered when using them together until more research is conducted.

Mannitol use in patients with renal replacement therapy

In patients with normal kidney function, mannitol is quickly excreted through urine. Kaufmann and Cardoso[27] demonstrated in an animal study that mannitol was rapidly removed from the plasma even when it was administered repeatedly every 4 hours. However, mannitol accumulation was reported in some brain regions and edematous white matter. These findings suggest that in patients with impaired kidney function, mannitol may not be excreted and could remain in the plasma for an extended period, potentially accumulating in brain tissue at damaged BBB sites.

In patients undergoing hemodialysis, the ICP-reducing effects of mannitol or HTS are effective.[13,14,24] While peritoneal dialysis is not efficient at removing mannitol, hemodialysis can effectively eliminate it. Additionally, mannitol accumulated in brain tissue can also be removed through hemodialysis (**TABLE 1**).

CLINICAL USE OF MANNITOL

Administration guide

Mannitol administration can be guided by ICP monitoring, administered when a specific ICP level is higher (ICP-directed), or based on changes in the clinical condition (imaging-clinical examination (ICE)-based). In some cases, mannitol is administered at fixed time intervals for a certain period, regardless of the above changes (scheduled).

Each method of mannitol administration, including ICP-directed, ICE-based, and scheduled administration, has been studied in various clinical situations. Here's a brief summary of these administration methods in different clinical scenarios:

TABLE 1. Summary of administration of method of mannitol

Variables	Detail
Bolus vs. Continuous	Bolus > Continuous
Rate of infusion	Over 15–30 minutes, not exceeding 0.1 g/kg/min
Dose	0.5–1.5 g/kg (avoid osmolar gap >55 mOsm/kg, >200 g/day)
Renal replacement	Using Hemodialysis or on CRRT (not recommend peritoneal dialysis)
Combination with HTS	No specific recommendation

CRRT: continuous renal replacement therapy, HTS: hypertonic saline.

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Traumatic brain injury (TBI)

The 2017 Brain Trauma Foundation guidelines do not provide recommendations on mannitol administration.[5] There was no class I evidence to recommend a specific administration method. However, ICP monitoring has been shown to improve in-hospital mortality and 2-week post-injury mortality in severe TBI patients (level IIB evidence).[5] In situations where ICP monitoring is available, ICP-directed treatment can help improve mortality and prognosis. If ICP monitoring is not possible, scheduled mannitol administration is recommended.

- ICP-directed: Studies have shown that using mannitol in an ICP-directed manner can help improve mortality and prognosis when ICP monitoring is available.[7]
- ICE-based: Results are conflicting and inconclusive.
- Scheduled: May be recommended if ICP monitoring is not possible due to resource allocation or equipment failure.[6]

Spontaneous intracerebral hemorrhage (sICH)

The 2022 American Stroke Association/American Heart Association ICH guideline suggests that treatment based on ICP monitoring can reduce mortality and improve prognosis in moderate to severe sICH/intraventricular hemorrhage with decreased consciousness (Class IIb evidence).[21] Early prophylactic scheduled mannitol administration in sICH patients is controversial.[47] In sICH patients with decreased consciousness, ICP-based mannitol administration can be expected to have a good prognosis. If ICP monitoring is not possible, ICE-based treatment is recommended instead of scheduled mannitol administration.

- ICP-directed: Can be expected to have a good prognosis in sICH patients with decreased consciousness.
- ICE-based: Recommended when ICP monitoring is not possible, as scheduled mannitol administration may cause neurological deterioration.
- Scheduled: Controversial, as it may increase mortality and not be advantageous for improving neurological symptoms.

Ischemic stroke

Mannitol is recommended in several guidelines for ischemic stroke. Osmotic therapy, including mannitol, is recommended for patients with worsening ICE-based clinical symptoms due to cerebral edema associated with ischemic stroke.[8,37] However, scheduled mannitol administration is not recommended due to uncertain effects on functional prognosis and potential increased mortality.

- ICE-based: Osmotic therapy, including mannitol, is recommended for patients with worsening clinical symptoms due to cerebral edema associated with ischemic stroke.
- Scheduled: Not recommended due to uncertain effects on functional prognosis and potential increased mortality.[48]

Subarachnoid hemorrhage (SAH)

While osmotic therapy is proposed based on neurological outcomes in ICE-based studies, this evidence primarily uses HTS rather than mannitol.[8] Mannitol use may increase the risk of cerebral vasospasm due to its diuretic effects, leading to hypovolemia.[2] However, there is still insufficient evidence to strongly support the use of specific medications.

- ICE-based: Osmotic therapy is proposed based on neurological outcomes, but the evidence primarily uses HTS rather than mannitol.
- Specific recommendations for ICP-directed and scheduled administration in SAH are not well-established due to insufficient evidence.

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Brain tumors

Mannitol injection can exacerbate vascular cerebral edema in brain tumors by redistributing it into the brain parenchyma through the damaged BBB.[26] Mannitol use can be supported only in cases of rapid ICP elevation due to brain tumor, but empirical use of mannitol is not recommended without clinical or numerical evidence of ICP elevation.[18]

- Rescue concept: Mannitol use can be supported only in cases of rapid ICP elevation due to brain tumor.
- Empirical use without clinical or numerical evidence of ICP elevation is not recommended.

These findings illustrate that the optimal administration method for mannitol depends on the specific clinical situation and evidence.

Clinical threshold monitoring methods for mannitol use

ICP monitoring

This method is essential in cases with increased space-occupying lesions that can cause secondary nerve damage, brain herniation, or brain death. Treatment should be guided by ICP, clinical symptoms, and brain computed tomography findings.[5] Setting the ICP threshold below 22 mmHg (18 mmHg in female and elderly patients) can reduce mortality and improve CPP.[46] The pressure reactivity index threshold is also useful for mortality reduction and favorable outcomes.

OG

This method considers the blood osmotic pressure when administering mannitol, as the risk of mannitol-induced renal failure increases when blood osmotic pressure is 320 mOsm/kg or higher.[17] The plasma OG accounts for the pure effect of mannitol on blood osmolality and has a higher correlation with the degree of mannitol accumulation in plasma. Many studies have confirmed that the rate of renal failure due to mannitol administration is low when the OG threshold is set at 55 mOsm/kg.[19]

OG can be calculated using the following formula:

$$\begin{aligned} &\text{OG}=\text{Measured Osmolarity}-\text{Calculated Osmolarity} \\ &=2\times(\text{Na [mmol]})+1.15\times(\text{Glucose [mg/dL]})/18+(\text{BUN [mg/dL]})/2.8 \end{aligned}$$

Although mostly in the retrospective studies or case reports, many studies have confirmed that the renal failure due to mannitol administration is low when the OG threshold is set below 55 mOsm/kg.[38,51]

EVIDENCE-BASED RECOMMENDATIONS OF MANNITOL

Summary of suggested use of mannitol are detailed in the **TABLE 2**.

MANNITOL-RELATED COMPLICATIONS

Kidney injury

AKI caused by mannitol, which is used to treat increased ICP, has been reported to occur in about 6-12% of cases. The incidence is known to increase in patients with diabetes, heart failure, a history of kidney disease, and those using diuretics.[8] AKI is defined as an increase

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TABLE 2. Evidence-based recommendations for clinical use of mannitol

Recommendations	COR	LOE
Hyperosmotic therapy may help reduce ICP elevation or cerebral edema in patients with SAH, TBI, AIS, ICH, and HE.	2b[8]	C (LD)
The neurological improvement of prophylactic hyperosmotic therapy in patients with spontaneous ICH has not been established.	2b[21]	B (NR)
Temporary hyperosmotic therapy can be considered to promptly reduce ICP in patients with spontaneous ICH.	2b[21]	C (LD)
In patients with progressive neurologic deficits due to cerebral edema accompanying cerebral infarction, hyperosmotic therapy can be used and does not induce midline shift.	2a[37,48]	C (LD)
Although hyperosmotic therapy can lower ICP, there is insufficient evidence to support specific recommendations and the use of specific hyperosmolar agents in patients with severe TBI.	2b[5]	B (NR)
High-dose mannitol (minimum 1.2–1.4 g/kg) may be used in comatose trauma patients with preoperative acute subdural hematoma or intraparenchymal temporal lobe hemorrhage.	2a[10]	C (LD)
Hyperosmotic therapy is not routinely recommended for patients with brain tumor edema.	3[18,26]	C (EO)
Mannitol can be used empirically in the setting of trauma and SAH to control elevated ICP.	2b[2]	C (EO)
The use of mannitol as a continuous intravenous infusion is not recommended.	2b[8]	C (LD)
Routine infusions of hyperosmotic therapy (e.g., every 4 or 6 hours) are not recommended without clear evidence of elevated ICP.	2b[8]	C (LD)
It is recommended to maintain a serum osmolality <320 mOsm/kg.	2b[8]	C (LD)
When the OG is 20–55 mOsm/kg, mannitol should be used with caution for renal damage, and dosing is not recommended when the OG is 55 mOsm/kg or higher.	2b[8]	C (LD)
Below the serum sodium range of 155–160 mEq/L, the serum chloride range of 110–115 mEq/L it is recommended to control serum sodium and chloride levels to reduce the risk of acute renal injury.	2b[8]	C (LD)
Hyperosmolar therapy, per se does not affect neurological prognosis or outcome.	2b[8]	B (NR)

COR: class of recommendation, EO: expert opinion, ICP: intracranial pressure, SAH: subarachnoid hemorrhage, TBI: traumatic brain injury, AIS: acute ischemic stroke, ICH: intracerebral hemorrhage, HE: hepatic encephalopathy, ICP: intracranial pressure, OG: osmolar gap, LD: limited data, LOE: level of evidence, NR: non-randomized.

in creatinine concentration of 0.3 mg/dL or more, or about 50% of the baseline level.[40,49] The mechanism of kidney injury is believed to be due to constriction of afferent arterioles caused by mannitol administration and a hypovolemic state resulting from excessive diuretic action. Histological changes include vacuole formation and edema of tubular cells in the proximal tubule, leading to kidney damage due to injury to the renal medulla from acute tubular necrosis.[29] The risk of such kidney damage increases if a high dose of mannitol is used, or dehydration, hypotension, or hypovolemia persist.

On the other hand, mannitol is also known to protect kidney function. Since mannitol filtered by the kidneys is not reabsorbed and remains in the renal tubules, it increases sodium transport to the distal tubules, causing persistent osmotic diuresis. This caused the protective effect by producing a 'flushing' effect in the tubules that can reduce the accumulation of necrotic cells.[43] As mentioned earlier, mannitol is known to have both kidney toxicity and protective effects. To prevent kidney toxicity, it is important to maintain normo-volemic hyperosmolar state. To achieve this, if urine output increases due to osmotic diuresis caused by mannitol administration, physiological saline should be administered to maintain normal blood volume.

In addition, blood osmolality is often tested to monitor the amount of mannitol in plasma, but it is more useful to check the osmotic gap between the actual measured osmolality and the calculated osmolarity. The osmotic gap is known to have a higher correlation coefficient with the mannitol blood concentration than osmolality. Generally, if osmotic gap is 20 mOsm/L or higher, it is recommended to withhold mannitol administration. However, if aggressive ICP is required, mannitol can be carefully administered while monitoring osmotic gap up to 55 mOsm/L.[8] The timing for blood test for monitoring is before administering the next dose of mannitol. If it takes 1 hour to confirm the test result, a blood test is performed 1 hour before administering the next dose of mannitol, and the decision to administer the next dose can be made based on the result. Tests to check for electrolyte imbalances or acid-base imbalances mentioned above can also be performed at this time.

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Hypotension

Rapid administration of mannitol can lead to hypotension, as it can reduce peripheral vascular resistance and cause osmotic diuresis, which decreases intravascular volume in the body.[49] In patients with elevated ICP, the occurrence of hypotension may cause additional brain damage by lowering CPP. According to a study investigating the relationship between mannitol and hypotension, when blood pressure was measured every 15 minutes after injecting mannitol over a period of 10 to 20 minutes, the blood pressure reduction effect was not statistically significant, but the ICP reduction was significant.[49] Based on this, avoiding rapid infusion of mannitol in less than 5 minutes can reduce the occurrence of hypotension. Therefore, it is recommended to control the administration rate of mannitol so that it does not exceed 0.1 g/kg/min over a period of 15 to 30 minutes.

Electrolyte disturbances

The effect of mannitol on blood electrolytes may vary depending on the time of examination after injection or the general condition of the patient. Immediately after injecting mannitol, the amount of water in the blood vessels increases due to the rise in plasma osmolality, resulting in a temporary decrease in blood sodium concentration (hyponatremia). This is due to the dilution of sodium caused by the increase in blood volume in the blood vessels. Additionally, when mannitol accumulates in blood vessels in patients with existing kidney dysfunction or when high-dose hypertonic mannitol is injected, osmotic movement of water and potassium out of the cells occurs due to an increase in plasma osmolality, like that produced by hyperglycemia. This results in extracellular fluid volume expansion, pulmonary edema, hyponatremia, metabolic acidosis (dilution of bicarbonate), and hyperkalemia.

In the next phase of action, mannitol is freely filtered by the glomerulus and is not reabsorbed in the tubules. Thus, it acts as an osmotic diuretic and increases urinary loss of sodium and water. If additional fluid loss is not compensated for, dehydration and hypernatremia may result. Therefore, careful electrolyte monitoring is required when using mannitol.[43]

As the duration of mannitol administration increases, sodium concentration may decrease or, conversely, increase. The decrease in sodium concentration (hyponatremia) is presumed to be due to increased excretion through the kidneys. On the other hand, the increase in concentration (hypernatremia) may be due to the concentration effect caused by dehydration or the sodium content of the saline solution infused to maintain normal blood volume.

In the case of potassium, it is common for the blood concentration to decrease when the administration period is prolonged, but the blood concentration may rather increase when kidney function is decreased. As such, since mannitol administration can cause various electrolyte abnormalities, active electrolyte monitoring is required.

Rebound effect

The rebound effect refers to a phenomenon in which mannitol, injected to treat cerebral edema, instead causes cerebral edema. This occurs because, when the osmotic reflection coefficient of mannitol is 0.9, about 10% can leak into brain tissue when administered, and the leakage can become more severe in patients with a compromised BBB.[28] Mannitol accumulated in brain tissue creates a reverse osmotic pressure gradient, resulting in brain edema.

Additionally, because of long-term osmotic therapy, brain cells accumulate electrolytes such as sodium, potassium, and chloride from extracellular fluid, cerebrospinal fluid, and

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blood to adapt to the surrounding high osmotic environment. Over time, matrix osmotic substances gradually accumulate in brain cells, including glutamate, glutamine, and urea. When mannitol is abruptly discontinued in this new steady state, intracellular electrolytes initially escape out of the cells, and matrix osmotic substances also decrease. However, in the meantime, brain cells have a relatively high osmotic pressure compared to the surrounding tissue fluid and blood, leading to cell swelling.[36]

However, clinically, it is not common to encounter cases brain edema is paradoxically worsened due to the penetration of mannitol into brain tissue at the beginning of administration. When stopped slowly, the rebound effect is rare.[49] Nonetheless, in cells and vascular edema where damage to the BBB is prominent, continuous administration of mannitol in this environment can cause mannitol and matrix substance accumulation. Therefore, intermittent administration of mannitol can help prevent the rebound effect.

Mannitol-associated hyperglycemia

It is a condition that primarily affects elderly patients with type 2 diabetes who have limited water intake. This complication is characterized by a decrease in extracellular fluid due to hyperglycemia in a state where insulin's effect is reduced, leading to hyperosmotic pressure and electrolyte abnormalities. In the case of mannitol use, if a patient with insulin deficiency experiences hyperglycemia alongside hyperglycemia, osmotic diuresis can occur due to continuous mannitol administration, and if dehydration progresses, hyperglycemia and hyperosmolality may worsen. It presents as severe dehydration, hypotension, and tachycardia and may be accompanied by altered consciousness. Test findings show hyperglycemia (>600 mg/dL) and hyperosmotic pressure (>320 mOsm/kg), and treatment involves correction with intravenous fluids and insulin administration.

CONCLUSION

This review aims to enhance the understanding of mannitol's role in managing increased ICP by examining various aspects of its administration. By synthesizing recent research and clinical experiences, we strive to provide a comprehensive insight into effective mannitol usage, ultimately improving therapeutic strategies and patient outcomes. Further investigation is necessary to address crucial questions surrounding optimal infusion rates, dosing strategies, fluid replacement plans, and monitoring techniques, thereby refining mannitol application, and informing future research directions.

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