

Systematic Review of the Role of Mannitol in Renal Diseases

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Abstract Mannitol, a novel osmotic agent and natural polyol extensively, is sometimes effective in reversing acute renal injury, but it can also induce the acute renal tubular injury. The role of mannitol in kidney is controversial. It is a small particle, distributed only in the extracellular space, is freely filtered at the glomerulus, and is not reabsorbed by the tubules. This systematic review was conducted to sum up the association of mannitol with renal diseases. The mannitol may precipitate acute renal failure if serum osmolality exceeds 320 mOsm/L, but the lower concentration might be positive. However, more studies should be performed in the future.

Keywords: mannitol, osmotic diuretic, osmotic nephrosis, acute renal failure, systematic review

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1. Introduction

Mannitol a novel osmotic agent and natural polyol extensively, is sometimes effective in reversing acute brain swelling, but its effectiveness in the ongoing management of severe head injury remains unclear. There is evidence that, in prolonged dosage, mannitol may pass from the blood into the brain; however, it might cause increased intracranial pressure [1]. As the same as that, mannitol is sometimes effective in reversing acute renal injury, but it can also induce the acute renal tubular injury. Mannitol has been administered during partial nephrectomy as a renal protective agent for ischemic damage [2]. However, the role of mannitol in kidney is controversial.

Mannitol is the reduced form of the 6 carbon sugar, mannose. It is a small particle, distributed only in the extracellular space, is freely filtered at the glomerulus, and is not reabsorbed by the tubules. It is pharmacologically inert, essentially not metabolized, and nontoxic within wide dosage limits. Since mannitol can not be reabsorbed it must traverse the length of the nephron, within the tubule, carrying with it the fluid it obligates. The excretion of mannitol and its obligated fluid constitutes an osmotic diuresis. Solutes such as urea, hypertonic glucose, and sodium chloride are less suited for the purpose of osmotic diuresis because of their more extensive distribution, tubular reabsorption, and metabolism. Still, until just recently, mannitol had been used almost exclusively in the research laboratory. When it was used clinically, dosage was variable and its value as an osmotic diuretic was not appreciated [3].

2. Materials and Methods

2.1. Search Strategy for the Role of Mannitol in Renal Diseases

Relevant studies were extracted from the electronic databases of PubMed on December 1, 2013. The retrieval strings entered into these databases were: "mannitol AND (renal OR kidney)". Additional reports were identified by scrutinizing the references cited in the recruited articles.

3. Inclusion and Exclusion Criteria

Inclusion criteria: (1) The outcome had to be renal diseases; (2) The investigation should provide the data or the conclusion on the effect of mannitol on renal diseases.

Exclusion criteria: (1) Preliminary results not on mannitol or renal diseases; (4) Investigation of the role of mannitol related to other diseases.

3.1. Protective Role of Mannitol in Renal Diseases

In vitro and in vivo research has focused on postulated mechanisms by which mannitol might be effective in preventing acute renal failure (ARF) following rhabdomyolysis. The proposed mechanisms involve extrarenal and renal actions of mannitol that go beyond the promotion of diuresis. Possible mechanisms include reducing skeletal muscle cell edema, dilating glomerular capillaries, stimulating prostaglandin E and I release, reducing tubular cell swelling, and hydroxyl radical scavenging effects. Various publications have placed more weight on one or more of these listed mechanisms [4]. The effect of mannitol on acute renal injury induced by ischemia/reperfusion of lower limbs in rats was studied, and the experiment clearly indicated that the lower limbs ischemia/reperfusion induced acute renal injury attenuated

significantly by mannitol treatment [5]. Ischemia / reperfusion of the rat pancreas evokes immediate renal dysfunction. Kidney oxidant-antioxidant balance is disturbed, but can be prevented with mannitol [6]. Sirivella et al [7] conducted a study in one hundred patients with postoperative oliguric or anuric renal failure despite adequate postoperative cardiac output and hemodynamic function, and reported that infusion of solution of mannitol, furosemide, and dopamine promoted diuresis in patients with acute postoperative renal failure with adequate postoperative cardiac output and had decreased the need for dialysis in the majority of patients. Early administration of this solution in acute renal failure caused early restoration of renal function to normal or baseline status.

3.2. Risk Role of Mannitol in Acute Kidney Injury

Acute kidney injury (AKI) is common in hospitalized patients and is associated with significant morbidity and mortality, and the incidence of AKI is increasing and despite clinical advances there has been little change in the outcomes associated with AKI [8]. Mannitol is widely used to reduce intraocular pressure and intracranial pressure. The major nephrotoxicity of mannitol is the injury to the tubule such as swelling of proximal tubular cells and vacuolization, the so-called osmotic nephrosis. Tsai et al [9] reported that mannitol-induced ARF with hypertonic hyponatremia in clinical practice. A 62-year-old man was admitted to the ophthalmologic department for operation of retinal detachment, and mannitol was prescribed to reduce intraocular pressure. Seven days after operation, gradual onset of drowsy consciousness occurred, and the laboratory findings of hypertonic hyponatremia, hyperosmolality, metabolic acidosis and acute renal failure dictated a diagnosis of mannitol-induced acute kidney injury. Fang et al [10] retrospectively studied a random cohort of 171 patients with cerebral trauma to investigate the risk factors of AKI following cerebral trauma, and found that the accumulative doses of mannitol were independent risk factors of AKI. ARF induced by mannitol is a lethal adverse effect, and hemodialysis or plasma exchange is recommended to avoid fatal ARF. Kouki et al [11] reported one case of ARF caused by mannitol. The case was a 56-year-old man with diabetes mellitus (DM) and chronic renal failure (CRF), was admitted with acute glaucoma. Mannitol was given to reduce the eye pressure. On the third day, mannitol was discontinued immediately, since his serum creatinine increased from 1.25 mg/dL to 6.43 mg/dL. Majumdar et al [12] performed a randomized controlled trial to study the forced euvolemic diuresis with mannitol and furosemide for prevention of contrast-induced nephropathy in patients with chronic kidney disease (CKD) undergoing coronary angiography. In the two hours before angiography, all study patients received at least 500 mL of half-normal saline plus 15 mmol of potassium chloride. Before the procedure itself, intervention or control intravenous study solutions were started and run at a standard rate of 125 mL/h for the next 4 hours. The intervention solution consisted of 500 mL of half-normal saline, 15 mmol of potassium chloride, 25 g of mannitol, and 100 mg of furosemide. The intervention and control study bags were run until completed, taking 4

hours in total. They found that contrast-induced nephropathy occurred in 23 (50%) intervention patients versus 13 (28%) controls. They also performed a meta-analysis included three studies and reported that furosemide-based interventions lead to significant harm compared with hydration. Redfors et al [13] evaluated the effects of mannitol on renal oxygen consumption (RVO_2), renal blood flow (RBF) and glomerular filtration rate (GFR) in postoperative patients of cardiac surgery. Mannitol infusion (225 mg/kg + 75 mg/kg/h) and combined mannitol and furosemide infusion (0.25 mg/kg + 0.25 mg/kg/h) were used in this study. In patients with normal renal function, mannitol increases GFR, which increases tubular sodium load, sodium reabsorption and RVO_2 after cardiac surgery. The lack of effect on RBF, indicates that mannitol impairs the renal oxygen supply/demand relationship. Furosemide normalised renal oxygenation when combined with mannitol. The high frequency of apoptosis correlated significantly with the increase in the osmolality of the mannitol in acute renal damage [14].

3.3. No Significant Effect of Mannitol on Renal Diseases

Mannitol has been administered during partial nephrectomy as a renal protective agent for ischemic damage. However, Omae et al [2] performed a retrospective study in 55 patients who underwent open partial nephrectomy for renal cancer in a solitary kidney, and there might be no advantage from the administration of mannitol during open partial nephrectomy. Of the 55 patients, mannitol was given to 20 patients (group M+) and not to the other 35 patients (group M-). Mannitol made no significant difference in both the postoperative estimated GFR and its decrease rate at any point within 6 months of the postoperative period. The incidence of acute kidney injury requiring dialysis was one (5.0%) in group M+ and two (5.7%) in group M-. Smith et al [15] studied 50 patients having cardiac surgery with serum creatinine between 130 and 250 $\mu\text{mol/L}$. Patients were randomised to receive mannitol 0.5 g/kg, or an equivalent volume of Hartmann's solution, in the bypass prime. There were no differences between the groups in plasma creatinine or change in creatinine from baseline, urine output, or fluid balance over the first three postoperative days. They conclude that mannitol has no effect on routine measures of renal function during cardiac surgery in patients with established renal dysfunction. Mannitol is often added to the cardiopulmonary bypass pump prime to reduce the incidence of renal dysfunction, but studies so far have been inconclusive. Yallop et al [16] performed a double-blind, randomised, controlled trial in cardiac surgical patients with pre-operative plasma creatinine < 130 $\mu\text{mol/L}$. Twenty patients received 0.5 g/kg of mannitol in the pump prime, whereas 20 control patients received an equivalent volume of Hartmann's solution. Blood and urine samples were taken on the day before surgery and daily for 5 days postoperatively for measurement of plasma urea and creatinine, urinary creatinine, retinol binding protein and microalbumin. They found no differences between the mannitol and control patients for any measured variable, and conclude that mannitol has little impact on renal function in patients with normal pre-operative plasma creatinine concentrations.

4. Conclusions and Perspectives

Mannitol is an intravascular volume expander that can also function as a free radical scavenger, as well as an osmotic diuretic. This is thought to be due to the release of intrarenal vasodilating prostaglandins and atrial natriuretic peptide, which decreases intravascular cell swelling and renin production. However, does a higher value of renal blood flow at any given perfusion pressure benefit the kidney? This might not be correct. Kidneys receive approximately 20% of cardiac output, but consume only approximately 10% of total body oxygen uptake; and the medulla receives just 6% of the total renal blood flow. Furthermore, the pO_2 in the medulla is normally approximately 10 mmHg versus 50 mmHg in the cortex. That is why renal blood flow increased by mannitol might have no impact on the oxygen supply to the medulla [2]. Furthermore, mannitol did not affect cardiac index or cardiac filling pressures in early ischemic acute kidney injury after cardiac surgery, but mannitol increased urine flow by 61%, accompanying by a 12% increase in renal blood flow and a 13% decrease in renal vascular resistance. Mannitol increased the renal blood flow/cardiac output relation. Mannitol caused no significant changes in renal oxygen extraction or renal filtration fraction [17].

Which concentrations of mannitol can induce the AKI? It should be investigated in the future. Mannitol is effective and has been used for decades in the treatment of traumatic brain injury, but it may precipitate acute renal failure if serum osmolarity exceeds 320 mOsm/L [18]. However, Malek et al [19] indicated that exposure to incremental osmolar concentrations of 300 mOsm of each osmotic agent increased apoptosis in bovine aortic endothelial cells. Malek et al [19] had shown that hypertonic mannitol exposure induces endothelial cell apoptosis, accompanied by activation of tyrosine and stress kinases, phosphorylation of FAK and paxillin, and elevation of intracellular free $[Ca^{2+}]$. The serum osmolarity exceeds 320 mOsm/L might induce the osmotic nephrosis, but more studies should be performed in the future.

How to prevent the osmotic nephrosis induced by mannitol? Treatment with hemodialysis in patients with established mannitol-induced osmotic nephrosis leads to accelerated removal of mannitol from the extracellular space and may shorten the recovery time from AKI [20].

Mannitol is a double-edged sword in renal diseases. It should be used reasonably in patient with and without renal diseases.

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Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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