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Examining Mannitol Use in Kidney Cancer Surgery: A Cautionary Tale of Extrapolated Surgical Data

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Keywords

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1. Introduction

Maintaining adequate renal function is critical to physiologic homeostasis and important to survival [1]. A link is recognized between renal dysfunction and overall medical comorbidity, including cardiovascular illness; however, it is self-evident that there is a distinction between medical renal disease and iatrogenic renal dysfunction that may result from renal trauma or surgery. There is unsettled controversy as to a reverse causal relationship between renal dysfunction and cardiovascular toxicity, implying that iatrogenic chronic kidney disease (CKD) results in cardiovascular or other medical comorbidity, although no direct causal relationship has clearly been demonstrated, only an association between the two conditions that often co-occur. Regardless, a fundamental medical principle is to preserve renal function and prevent deterioration when possible, further understanding that management in circumstances where renal function is threatened must address the underlying driving mechanisms of injury.

Changes in renal function following different forms of kidney surgery can be multifactorial and dependent on aspects such as subtype of pre-existing medical renal disease, physical loss of functional parenchyma, collateral traumatic renal injury, vascular injury, postsurgical hypotension, hyperfiltration, cold perfusion injuries (as seen in renal allografts after cold hypertonic flush), and immune-mediated diseases, among others [2]. Not enough is known

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regarding interplay of the myriad pre-existing contributing factors to functional recovery following kidney surgery, but from a practical perspective, kidney surgeons have attempted to develop uniform techniques to preserve renal function without compromising outcomes [3,4]. During procedures that may require temporary, in situ renal vascular arrest, such as aortic vascular repair, nephrolithotomy, and partial nephrectomy (PN), surgeons have employed empiric principles including organ hypothermia and limiting ischemia time with supporting evidence of measureable impact [5,6]. Several surgeons, many with renal transplant experience, have advocated the adjunctive use of the osmotic diuretic mannitol during PN, although clinical trials in renal ischemia do not support use for this purpose [7]. Cited rationale includes lack of harm, low cost, easy availability, and historically established practice despite a lack of demonstrated functional benefit, including level 1 evidence from recently performed phase 3 trials in PN. To address the current status of medical knowledge in this field, this review will focus on describing the mechanisms of action, clinical benefits, and risks of mannitol use in functional renal preservation.

2. Mannitol mechanism of action and ischemia reperfusion

Mannitol is a naturally occurring sugar alcohol that is water soluble and minimally absorbed when taken orally. Chiefly used as an intravenous osmotic diuretic, it is poorly metabolized and excreted freely through the glomerulus. Putative renal protective effects of mannitol were studied initially in animals to evaluate the impact on events associated with acute tubular necrosis (ATN) and ischemia reperfusion injury (IRI) [8,9]. Contemporary understanding of the pathophysiology of renal IRI and the severe associated consequence of acute kidney injury is highly complex, involving key aspects of cellular swelling, oxidative damage, reactive cytokines, mitochondrial dysfunction, and a cascade of inflammatory mediated tissue damage—and multiple linked events—that present several possible options for biologic targets, but only a few now support the use of mannitol [10]. Before many of these pathways were known, early interest in mannitol developed with the finding of increased renal blood flow and associated increased urine output when used in low doses [11]. Increased renal perfusion was found to occur predominantly in the renal cortex and less so in the medulla, ultimately shown to be produced by arterial vasodilation and reduced vascular restriction attributed to atrial natriuretic peptide [12] and prostacyclin [13]. With high mannitol doses the opposite can occur, producing severe vascular constriction. Isolated patient studies have failed to confirm significant changes in renal blood flow, particularly in the setting of hypovolemia, noting that post-diuresis hypotension may be a significant contributor to ATN following mannitol [12,14].

The accompanying osmotic diuretic effect overcomes renal tubule concentration ability, producing more isotonic urine felt to be beneficial in clearing tubular casts that contain cellular debris including the immunomodulatory Tamm-Horsfall protein [15–17], although potentially contributing to occasionally observed washout of the medullary solute gradient. The combined effect of increased renal blood flow and diuresis leads to a transient and artificial increase in glomerular filtration rate (GFR) [18], although this comes at the expense of increased metabolic load within the medulla as a result of increased urine production. Additionally, there is some supporting evidence that mannitol, similar to endogenous enzymes (eg, catalase, superoxide dismutase, etc.), substrates, and

macromolecules (eg, uric acid, bilirubin, albumin, etc.), may act as a scavenger of toxic-free radical species resulting from IRI, including hydroxyl radicals, thereby blunting deleterious effects in tissues such as cardiac and renal tissue [19,20]. These results are not entirely clear, and purported in vivo effects on free radicals have been disputed by animal [21,22] and human studies [23].

A large number of studies have been undertaken to explore how mannitol may be optimized or translated into human use, noting that dose- and species-dependent differences in renal effects have complicated this process when extrapolating animal data to provide bioequivalence in human application. As an example, large differences are evident comparing studies in a rat model, requiring doses of 3–5% body weight to demonstrate an increased GFR, whereas in dogs only 0.4–0.8% showed efficacy [24]. Along similar lines, dosing dependence within the same species in ischemia reperfusion models revealed that a dose of 0.25 g/kg had renal protective effects, whereas 2 g/kg impaired renal function [25]. Timing of administration has been a factor, as indicated by imaging and functional results demonstrating differences between infusions 30 and 15 min prior to ischemia [25,26], although mechanistic details are unclear in view of the known pharmacodynamic profile (rapid onset and clearance of roughly 2 h) perhaps, indicating different transient properties such as volume expansion and transient increased cardiac output [27]. Similar to the effects of urea, decreased renal tubular swelling has also been described when mannitol is given after reperfusion, although this observed feature is of unknown physiologic significance [28]. A differential impact of contralateral renal effects can also confound studies, whereas solitary kidney models may demonstrate a different pre-existing renal physiology and mannitol response in ischemia models [20,29]. Finally, it is notable that preclinical study results demonstrate only short-term physiologic shifts without a correlation to long-term functional benefits suggesting transient, artificial changes, as previously noted [30].

3. Clinical studies of mannitol for renal function preservation

3.1. Renal function preservation in PN

Mannitol use in PN is common globally, with no standardized guideline for use in this indication. Significant variability in practice including dosing regimens was reported in a recent survey indicating that 49% and 30% of urologists use 25 and 12.5 g in PN, respectively [7], starkly reflecting the absence of clinically useful information on utility and application. Physiologic equivalence, meanwhile, has been suggested in clinical studies using either dose [31].

A number of clinical studies have examined the utility of mannitol during PN, including a phase 3, double-blind randomized control trial of 199 patients with estimated GFR (eGFR) > 45 ml/min/1.73 m² who underwent PN and were randomized to receive intravenous mannitol or saline placebo at the time of surgery. At 6 wk and 6 mo, renal function outcomes in either group were similar, showing no significant difference [32]. These results were replicated in a single-surgeon randomized control trial of robotic PN of 79 patients using 12 g mannitol [33]. Additional retrospective investigations of single-center use of mannitol during PN have also failed to show benefit in eGFR with doses of 12.5–25 g [34,35].

Several criticisms have been raised, challenging the negative results of mannitol studies during PN. Assertions of possible functional benefits have been made in certain settings such as severe forms of CKD, concurrent use of furosemide, and higher doses of mannitol [36]. Additionally, hypothetical improvements in nephron viability could be seen without a measurable change in GFR, particularly in the presence of a normal contralateral renal unit. Mathematical models have estimated that a 50% decrease in GFR requires a four-fold reduction in glomeruli from baseline [37]. This was demonstrated in an animal model with mannitol, in which IRI led to a decrease of 1.14–0.89 million glomeruli without measurable change in GFR [29]. Solitary kidney models may offer some insight into renal compensatory change. A retrospective study of 55 patients undergoing open PN utilizing cold ischemia (average clamp time 51 min) used mannitol (20 g) administered before clamping compared with saline. No difference in postsurgical eGFR was identified at 6 mo from baseline [38]. In a follow-up study of the phase 3 trial, longer-term outcomes were evaluated, including the impact in patients with CKD—again showing no impact of mannitol [39].

3.2. Mannitol for renal function preservation in other clinical settings

The main source of evidence supporting that mannitol is for renal transplantation where graft function and failure are key concerns, particularly in the early post-engraftment period where renal dysfunction and ATN are often associated with rejection events or prolonged ischemia time [40]. Doses between 12.5 and 50 g mannitol with or without furosemide have been associated with decreased rates of ATN and longer-term renal preservation in renal grafts [31,41]. As described previously and for uncertain mechanisms, mannitol appeared to be more effective if initiated <15 min prior to arterial clamping, with no lower limit of time being established [31].

Mannitol does not appear to have a demonstrable advantage once ATN has developed in nonsurgical [42] as well postoperative patients [14,43]. A meta-analysis found that there was no benefit in cardiac surgery, noncardiac surgery, and nonrenal transplants with mannitol [44]. The majority of these studies included patients with normal renal function, and so conclusions regarding efficacy in patients with pre-existing renal dysfunction cannot be clearly determined; however, in a randomized control trial of 50 patients undergoing cardiac surgery with CKD (serum creatinine 130–250 $\mu\text{mol/l}$), mannitol at 0.5 g/kg did not prevent renal dysfunction [45]. Further studies evaluating renal preservation in patients with CKD exposed to radiocontrast media did not show a functional benefit in a randomized controlled trial using 25 g mannitol [46]. Additional investigations in CKD patients revealed that diabetic patients, compared with nondiabetics, failed to demonstrate an increase in renal blood flow and experienced an increased risk of nephropathy following mannitol infusion [47]. Further evidence of adverse functional outcomes with mannitol was seen in a randomized trial in CKD patients using 25 g mannitol with 100 mg furosemide for the prevention of radiocontrast-induced nephropathy, doubling the risk of renal failure within 48 h after infusion [48]. These data, while not directly applicable to IRI conditions, suggest that CKD patients may be vulnerable to physiologic disturbances following mannitol and furosemide use in combination with renal toxic events and require critical consideration when contemplating adjunctive pharmacologic management, which may have harmful effects.

4. Toxicity of mannitol administration

Mannitol is not a harmless compound, and its use at any dose level has been associated with severe renal and systemic morbidity, particularly in certain clinical scenarios. Volume expansion following initial infusion increases cardiac preload and may exacerbate heart failure [16]. Diuresis can mask hypovolemia, contributing to metabolic acidosis, hypotension, and electrolyte shifts including hypokalemia and hyponatremia. Multiple reports show acute renal failure secondary to large doses even in the setting of normal renal function or/and prior CKD [49–53]. Decreased renal blood flow due to renal vasoconstriction occurs with higher doses, provoking renal ischemia events and ATN. Repeat administration with lower dose (80 g/d) has been shown to lead to renal injury in patients with normal renal function and potential progression to hemodialysis requirement [54]. Osmotic nephrosis, whereby mannitol enters the cytoplasm and fuses with lysosomes, is one of the mechanisms of toxicity [55]. This process is especially important in diabetics and CKD patients. In addition, high doses of mannitol in vitro led to oxidative stress (contrary to free radical properties), apoptosis, and cytoskeleton destruction [56]. These processes may be uncommon or rare in patients managed for PN; however, any such related events would represent preventable harms that do not appear to be justified based on the current state of knowledge in the field.

5. Conclusion

Prospective clinical evidence from renal transplant studies suggesting a benefit of the use of mannitol for improving allograft function after renal transplant has not been replicated in the in situ IRI setting during PN in patients with normal presurgical renal function. In this case, it is not possible to recommend continuous use for this purpose. The efficacy of mannitol in PN in patients with particular risk factors such as CKD has not been investigated sufficiently to ascribe potential benefits to it, particularly when retrospective studies in CKD patients have not shown efficacy. The state of knowledge on the pathophysiology of renal IRI has advanced significantly since the use of mannitol as an osmotic diuretic was first investigated as a renal protective agent and targetable pathways have been implicated, which may be appropriate for prospective studies to better address ischemic injury during PN.

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