Current Urology Reports (2019) 20: 6
https://doi.org/10.1007/s11934-019-0868-6

KIDNEY DISEASES (G CIANCIO, SECTION EDITOR)

Use of Mannitol for Ischemia Reperfusion Injury in Kidney Transplant and Partial Nephrectomies—Review of Literature

Jose Alejandro Lugo-Baruqui[1] · Rajinikanth Ayyathurai[2] · Adavan Sriram[2] · Kothai Divya Pragatheeshwar[3]

Published online: 26 January 2019

Abstract

Purpose of Review Few procedures involve the ischemia-reperfusion injury to organs purposely. Two clear examples in urologic surgery consist on kidney transplantation and partial nephrectomies.

Recent Findings Mannitol is an osmotic diuretic that is commonly used in partial nephrectomies and kidney transplantation to increase renal blood flow and decrease warm-ischemia-related renal injury to preserve estimated glomerular filtration rate (eGFR).

Summary We review the current evidence for the use of mannitol and its effects on these procedures.

Keywords Renal transplant · Mannitol · Ischemia-reperfusion injury · Partial nephrectomy

Introduction

Few procedures involve the ischemia-reperfusion injury to organs purposely. Two clear examples in urologic surgery consist on kidney transplantation and partial nephrectomies. Kidney transplant is the gold standard for the treatment of end-stage renal disease (ESRD). The outcome of the transplant depends largely on the quality of the kidney graft and management of ischemia/reperfusion injury (IRI) to prevent delayed graft function and long-term survival of the renal graft. In renal transplantation, IRI usually leads to primary renal dysfunction, delayed graft failure, increased late acute rejection, and allograft dysfunction. Modern imaging techniques lead to an increase in detection of incidental renal masses which are more frequently managed by partial nephrectomies (PN) [1]. National trend studies reported nephron sparing techniques being used in up to 32% of renal cancer surgeries [2]. With the advent of robot-assisted minimally invasive techniques, more partial nephrectomies are being performed under warm ischemia.

Mannitol is an osmotic diuretic that is commonly used in partial nephrectomies and kidney transplantation to increase renal blood flow and decrease warm-ischemia-related renal injury to preserve estimated glomerular filtration rate (eGFR). Mannitol is a polyol (sugar alcohol) used both in food and drug industry. Mannitol functions both as free oxygen radical scavenger and osmotic diuretic. In its pharmaceutical application, it can be found in a 10% or 20% concentration as intravenous infusion. Because of its low molecular weight (182 Da), it is excreted in the glomerulus; it cannot be secreted or absorbed in the tubules and draw osmotic gradient and increasing water excretion [3•]. Additionally, it causes the release of vasodilatory prostaglandins in the kidney causing vasodilation and increasing urinary flow [4, 5•]. Mannitol will increase intravascular volume, increasing tubular flow rate and preventing water absorption in the proximal tubule, increasing urinary output preventing cast obstruction in the tubules of the kidney. It is widely used as renoprotective agent in the setting of vascular and cardiac surgery, renal transplantation, and hepatic failure due to the high risk of renal complications. Lately, the benefits of mannitol in preventing ischemic renal injury are being questioned, and several studies have been published showing no clear benefit and possible adverse outcome with mannitol use in PN. We aimed to perform a

This article is part of the Topical Collection on *Kidney Diseases*

✉ Jose Alejandro Lugo-Baruqui
alejandro.lugo.b@gmail.com

✉ Rajinikanth Ayyathurai
uroayya@gmail.com

[1] Hospital Civil de Guadalajara "Fray Antonio Alcalde", Division of Transplant, Department of Surgery, University of Guadalajara, Guadalajara, Mexico

[2] Division of Urology, Northeast Georgia Medical Center, Gainesville, Georgia

[3] Department of Nephrology, University of Oklahoma, Tulsa, OK, USA

systematic review of literature on the role of mannitol in preserving renal function after Kidney transplant (KT) and partial nephrectomies (PN).

Use of Mannitol in Kidney Transplant

One of the primal factors in determining the quality of a renal graft for transplantation is the cold ischemia time which is the period in which the kidney graft is preserved before reperfusion in the new recipient. Living donor renal transplant provides shorter periods of cold ischemia time against deceased donors since donor and receptor surgeries are usually performed almost simultaneously. Prolonged cold ischemia time (CIT) elevates the risk of acute tubular necrosis (ATN) in the newly transplanted kidney due to a more severe ischemia-reperfusion injury. ATN prevention and management is critical since it is a detrimental factor for the survival of the renal graft in the acute and long-term period. Multiple interventions have been proposed to ameliorate the ischemia-reperfusion injury. One of the most widely applied worldwide is the administration of the osmotic diuretic mannitol both in donor and in the recipient.

As any other drug, mannitol has some adverse effects that need to be taken in consideration. The initial volume expansion of mannitol can exacerbate heart failure and pulmonary edema. The increased intravascular volume is quickly compensated with a diuretic effect that may cause dehydration and hypovolemia. This increased urinary output may cause electrolyte and acid-based disorders such as metabolic acidosis, hypernatremia, and hyperosmolar state. All these conditions need to be addressed in a patient with so many of these comorbidities as the end-stage renal disease patient on renal replacement therapy [6].

Several metabolic changes are present in the renal allograft after IRI including generation of free radicals. Some evidence suggests that the use of diuretics may ameliorate the damage caused by IRI. Part of the anesthesia protocol during a kidney transplant consists in fluid management and administration of diuretics to prevent low blood pressure or hypoperfusion in the new kidney graft as well as preventing lung edema in an anuric patient [6]. Mannitol is often used as a diuretic agent for this purpose and is administered before opening the vascular clamps for reperfusion of the renal allograft. Recent international survey by Cosentino et al. reported that 83% of the centers used mannitol (78.7 and 64.7% of centers performing partial and live donor nephrectomy respectively) [7]. Although this study revealed only the result of a survey, it is important to understand the ubiquitousness of mannitol application for renal protection. Another study reported immediate graft function and a glomerular filtration rate of only 30% inferior to the contralateral kidney in the donor in the first hour after completion of the transplant in patients managed with crystalloid fluid load, furosemide, and mannitol [8].

In an ischemia/reperfusion model with rats, mannitol was superior in terms of creatinine clearance, levels of neutrophil gelatinase-associated lipocalin (NGAL) and malondialdehyde (MDA). NGAL is a molecule frequently used in experimental models for detection of renal lesion and is elevated in patient on the waiting list for a renal transplant. As part of reperfusion injury, there are liberations of free radicals which damage the lipidic membrane of cells. Lipid peroxidation and cellular damage can be measured with MDA [9].

There is enough evidence to support the use of mannitol to prevent acute renal failure after transplantation [10]. The use of 250 ml of mannitol in 20% concentration given immediately before vessel clamp removal reduces the incidence of acute renal failure as indicated by lower requirements of posttransplant dialysis [11, 12]. In animal model of kidney and pancreas transplant, it was shown that the oxidant/antioxidant balance of glutathione and xanthine oxidase could be prevented with mannitol [13].

Ischemic insult after vessel clamping in renal procurement produces renal tubular cell swelling. This normothermic ischemic time varies from living to deceased donors. The hemodynamic protective effects of mannitol in this scenario include increasing renal blood flow and decreasing intravascular cellular edema and cell death. In a classic paper by Andrews et al. [14••], they observed with optical coherence tomography (OCT) that administration of mannitol 15 min prior to cross clamping in living kidney donor, the proximal convoluted tubules exhibited open lumens before transplant and showed a significant recovery of renal function after transplant vs patients with administration of the drug 30 min before clamping.

Nevertheless, few quality studies supporting the use of mannitol for a medicine-based stand point exist. Most studies are single center or with few numbers of patients. Detractors of the use of mannitol after reperfusion argue that the intervention may be futile. One study compared a group of kidney donors who received mannitol before clamping versus a control group with no mannitol with no significant improvement on renal function after transplant in the intervention group [15]. Excessive administration of mannitol may be harmful and result in dehydration and hypertonic kidney failure [16]. Arguments may fall in favor of other variables resulting more important in terms of renal function after transplant such as short cold and warm ischemia times, quality of the donor, and hemodynamic stability of recipient after reperfusion.

Use of Mannitol in Partial Nephrectomies

Where feasible, PN is the preferred approach for the management of renal cancers. PN has shown to decrease the risk of post-operative chronic kidney disease. Surgeons aim to preserve as many nephrons as possible by limiting the excision of normal kidney tissue and attempt to mitigate the adverse

effects of ischemia by reducing the clamp time and using renoprotective agents such as mannitol peri-operatively. As mentioned earlier, Cosentino et al. conducted an international survey across 47 centers on the use of mannitol during PN.

Seventy-eight percent of centers reported using mannitol during PN. Nearly half the centers used 25 g mannitol and another third used 12.5 g intravenously [7].

Power et al. published the results of a retrospective review in 2012 evaluating the effect of mannitol on postoperative eGFR [17]. Two hundred eighty-five consecutive patients who underwent elective minimally invasive PN were reviewed. Of these, 164 received mannitol and 121 did not. There was no difference in eGFR outcomes in patients who received mannitol. Patients who received mannitol tended to have a better preoperative eGFR, were more likely to undergo an ischemia, were more likely to be healthier and had less complex nephrometry score. Sensitivity analyses controlling the surgeon bias and cold irrigation during surgery did not provide any significant improvement on the post-operative eGFR.

Omae et al. studied 55 patients who underwent open PN for renal cancer in a solitary kidney and followed for 6 months post-surgery [18]. Twenty grams of mannitol was given intravenously 15 min before the renal artery clamping. Twenty patients received mannitol and 35 did not. The mean decrease in the eGFR was 49.3% and 46.9% at its nadir, and this recovered to 18.9% and 19.6% at 6 months after surgery in cohort receiving and not receiving mannitol respectively. The authors reported no significant differences in postoperative eGFR in both groups at any point during follow-up.

Spaliviero et al. published in 2018 the results of a prospective, randomized, placebo-controlled, double-blind, clinically integrated trial determining the effect of mannitol during PN [19]. Patients > 18 years of age with renal mass and preoperative eGFR > 45 were included and randomized in 1:1 fashion to receive mannitol (12.5 g) vs normal saline. Primary end point was difference in eGFR at 6 months post-surgery. Ninety-eight and 101 patients completed the trial in placebo and mannitol arms respectively. There was no significant difference in the primary end point or the duration of vascular occlusion between the two arms.

Choi et al. conducted a randomized, controlled, double-blinded, single surgeon prospective study which enrolled 35 and 30 patients who underwent robot-assisted laparoscopic PN and received 12 g mannitol or 50 ml of normal saline, respectively. eGFR was obtained preoperatively as well as postoperatively at 24 h, 1 week, and 30 days. Prospective analysis determined that infusion of mannitol does not impact the renal function after robot-assisted PN [20].

Well-conducted animal studies have supported the use of mannitol for its renoprotective effects. Green et al used rabbit kidney model to assess the effect of mannitol and showed that 0.25 g/kg of mannitol administered 15 min prior to warm ischemia was beneficial in reducing the effects of renal ischemia. In current surgical practice, mannitol is commonly used in nephron-sparing surgery despite its unproven benefits. Novick et al. did a systematic review on animal studies assessing the use of mannitol during PN and concluded that further studies are needed to assess the benefit of mannitol in the clinical setting [21]. However, no standard guidelines are available to guide urologists on mannitol usage to achieve optimal renoprotective effects.

Although animal studies have shown that mannitol increases renal blood flow, it is unclear if this translates into meaningful clinical benefit. In an editorial by Gelman on renal effects of mannitol, he reported that a differential increase in renal cortical blood flow with subsequent increase in GFR predisposes the renal medulla and the loop of Henle to be more susceptible to hypoxia-mediated injury [22]. Several other studies have documented acute kidney injury from high-dose mannitol use in renal transplant patients while aiming at osmotic dieresis. Intravenous mannitol extravasation leading to forearm compartment syndrome has been reported. Other medical specialties including vascular surgery and interventional cardiology have conducted controlled and uncontrolled clinical trials evaluating renal protective effects of mannitol and have shown no proven benefit in preventing postoperative decline in EGFR. Multiple randomized controlled trials have evaluated the effect of forced diuresis with mannitol and furosemide and have shown no proven benefit in preventing acute changes in renal function induced by radiocontrast agents.

Current realm of evidence does not support routine use of mannitol during PN. Both retrospective and prospective trials did not show significant advantage on protecting renal function by administering mannitol. As mentioned previously, Choi has done a well-designed single surgeon study which provides reasonable understanding of the limited benefit. Spaliviero et al. compared the scintigraphy findings of patients in both arms as an additional end point and did not find any significant difference in outcome with mannitol. Cooper et al. reported no benefit with mannitol infusion during the 476 partial nephrectomies [23]. Available studies have several caveats including the optimal dosage, time and rate of administration, hydration status of the patient, associated comorbidities, and limited follow-up.

Conclusion

Mannitol administration in kidney transplant is a widely used practice that has demonstrated potential benefit in decreasing IRI and prevention of ARF after reperfusion. Its administration must be carefully accompanied by adequate hydration to prevent the potential presentation of dehydration and acute kidney failure. Most evidence for its use in transplant comes from low evidence studies but since the potential benefit outweighs the adverse effects, the readily availability of the drug

in most transplant centers worldwide and common practice has made this intervention almost universal in transplant procedures either for living or cadaveric kidney grafts. Other factors should be given more weight in the outcome such as quality of the graft, short cold and warm ischemia times, and adequate management in the postoperative period.

The principal goal of PN is to preserve as much renal function. The recent RCT prospective studies provide level 1 evidence that routine use of mannitol does not offer protective benefit to postoperative renal function following PN with vascular clamping. Current evidence recommends discontinuing routine use of mannitol during PN in patients with normal preoperative renal function. However, further prospective studies are required to understand mannitol's beneficial role in patients with decreased renal function, prolonged vascular occlusion, and the dose-related benefit.

Compliance with Ethical Standards

Conflict of Interest Jose Alejandro Lugo-Baruqui, Rajinikanth Ayyathurai, Adavan Sriram, and Kothai Divya Pragatheeshwar each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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