



Intraoperative mannitol during robotic-assisted-laparoscopic partial nephrectomy

Kellen Choi¹ · Sharon Hill² · Nathan Hale² · Stephen Phillips³ · Samuel Deem²

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Abstract

Mannitol is routinely used during partial nephrectomies due to its renoprotective properties. With minimally invasive techniques, the need for mannitol has been questioned. Robotic-assisted laparoscopic partial nephrectomy (RALPN) has been shown to decrease warm ischemia time, which may potentially minimize the benefit of mannitol. To date, no prospective, randomized, controlled trials have investigated the use of mannitol in only robotic procedures. We hypothesize that the intraoperative mannitol use during RALPN provides no statistically significant benefit for post-operative renal function outcomes. We conducted a randomized, controlled, double-blinded, single surgeon, prospective study to assess renal function after RALPN. Patients were randomized into a control group with intravenous normal saline infusion prior to clamping of the vessels or to an experimental group with an infusion of mannitol. Estimated glomerular filtration rate (eGFR) were obtained prior to the surgery as well as post operatively at 24 h, 1 week, and 30 days. Preoperative eGFR showed no statistical differences between the groups and evaluation of median percent change in eGFR after surgery did not indicate a statistical difference between the groups after RALPN. After prospective analysis of the change in post-operative renal function of randomized groups who received 12 g of mannitol following RALPN, we determined that infusion of mannitol does not provide significant improvement of maintenance of renal functions after RALPN. Based on our results, we recommend discontinuing routine use of mannitol during RALPN.

Keywords Mannitol · Partial nephrectomy · Renal cell carcinoma · Renal mass · Prospective

Introduction

According to the American Cancer Society, 63,990 new cases of kidney cancer will be diagnosed in 2018 [1–3]. Increasingly, more localized small renal masses are being diagnosed due to the prevalent use of CT imaging for a variety of diseases and conditions. With the growing number of early detected small renal masses, partial nephrectomy

(PNx) will likely become increasingly common as well to treat and hopefully cure patients of renal cell carcinoma.

In addition to achieving the best oncologic outcomes, nephron sparing surgery should be of utmost importance. Nephron sparing is a key contributor to the preservation of renal function status post partial nephrectomy [4, 5]. Volpe et al. found 23% of patients in a large series to be stage 3 chronic kidney disease (CKD) or higher [5]. As partial nephrectomies become increasingly common to treat early detected small renal masses, surgeons need to be mindful of nephron sparing to prevent the development of chronic kidney disease and its associated comorbidities.

Mannitol is a naturally occurring sugar alcohol used as a means to medically preserve renal function during various surgeries, traditionally renal transplantation. It is believed to increase blood flow, decrease intravascular cellular swelling, increase free radical scavenging, and decrease renin production [5].

Use of mannitol is common, albeit highly variable among institutions due to the scarcity of high-level literature

✉ Samuel Deem
samuel.deem@camc.org

¹ Urology (Adult Office) at UofL Physicians Outpatient Center, University of Louisville, 401 E. Chestnut St., Suite 480, Louisville, KY 40202, USA

² Department of Urology, Charleston Area Medical Center, 3100 MacCorkle Avenue, Suite 602, Charleston, WV 25304, USA

³ Mount Nittany Physician Group, 905 University Drive, State College, PA 16801, USA

advocating its use in partial nephrectomies. Most literature comes from outdated information from transplant studies during the 1960s. Despite few high-level evidence studies done previously, Cosentino et al. [6] found that internationally 78% of high volume centers utilize mannitol during partial nephrectomies.

Review of the available literature finds that mannitol may not significantly preserve renal function during partial nephrectomy, especially with advances in surgical technology, utilizing robotic-assisted laparoscopic surgeries. Power et al. [4] retrospectively assessed 285 laparoscopic PNx over a 5-year period and found that 58% received mannitol with no significant long-term improvement or difference in renal function.

To date, there has been no double-blinded, randomized, prospective trial studying the effect of mannitol on renal function in robotic-assisted laparoscopic partial nephrectomies. We hypothesized that during robot assisted laparoscopic partial nephrectomy, the intraoperative infusion of mannitol solution does not significantly preserve renal function compared to normal saline infusion of the same volume. Minimal warm ischemia times are felt to mitigate its benefit in this setting.

Methods

Our study was initially a pilot study of a single surgeon, double-blinded, randomized, controlled trial comparing a control group who received 50 ml normal saline immediately prior to excision compared to an experimental group who was given 12 g mannitol in 50 ml normal saline. Approval for this study was obtained through the Charleston Area Medical Center Institutional Review Board.

Exclusion criteria included patients younger than 18 years old, eGFR < 45, solitary kidney, tumor > 7 cm, and an allergy to mannitol. Randomization schedule was created using SAS 9.3 and provided to CAMC Pharmacy to keep surgeon and patient blinded of assignment. Once surgeon enrolled patient, pharmacy was notified to provide blinded drug and keep list of assignments for future analysis. Additional data collection including demographics, comorbidities, tumor characteristics, surgical assessment, and other intraoperative measures were obtained.

Primary outcomes of this study were eGFR at 24 h, 1 week, and 30 days. Secondary outcomes were percent change in eGFR at 24 h, 1 week, and 30 days, as well as complication and readmissions.

Sample size calculation for the primary outcome indicated 16 patients in each group were required to have 80% power of detecting a difference of 5 ml/min/1.73 m² in eGFR. A descriptive analysis of the study groups was performed using means, standard deviations, ranges and

percentages. Subgroup comparisons examined differences in the percent change of eGFR post-surgery. Continuous variables were analyzed using the Student's *t* test and categorical variables using Fisher's Exact Test with a $p < 0.05$ considered statistically significant.

At the time of the study, our single surgeon (Deem) had performed greater than 250 robotic partial nephrectomies and had previously been a proctor of the procedure for Intuitive Surgical. Standard clamping was performed at pedicle during time of the robotic-assisted laparoscopic partial nephrectomy. This included placement of one Bulldog clamp on each artery and vein. Other factors such as tumor complexity and location were evaluated using nephrometry score.

Results

79 patients were enrolled with 65 completing the analysis. They were enrolled from Oct 2013 to Oct 2016. Patient demographics and comorbidities were reviewed. BMI was statistically higher in the control group. Tumor characteristics and nephrometry score were not significantly different between the two groups. Intraoperative blood loss was higher and systolic blood pressure was increased in the control group.

Mean preop creatinine was not significantly different between the two groups. Mannitol administration was not found to significantly improve primary or secondary renal functional outcomes. No significant differences were found for mean eGFR at 24 h, 1 week, or 30 days. No significant difference was found in the percent change of eGFR at 24 h, 1 week, or 30 days. Complications and readmissions were negligible. The two readmissions were due to a hematoma and an ileus. They both occurred within the first 4 weeks of surgery and resolved with conservative management. Of note, the patient who was readmitted for an ileus also had a concomitant laparoscopic cholecystectomy. One patient had bilateral renal masses so was enrolled twice for the study and accounts for the second surgery on mannitol group.

Mean warm ischemia time was 10.7 min in the mannitol group and 11.2 min in the saline group (Tables 1, 2; Fig. 1).

Discussion

Renal masses are presenting with increasing frequency in younger populations. Improvement in access to surgical oncologic care with nephron sparing is pivotal. Increased warm ischemia time has been found to play a role in post-operative reduction of renal function, due to hypoxic injury and free radical formation [6, 9]. In an attempt to maximize renal function intraoperatively, mannitol has been used

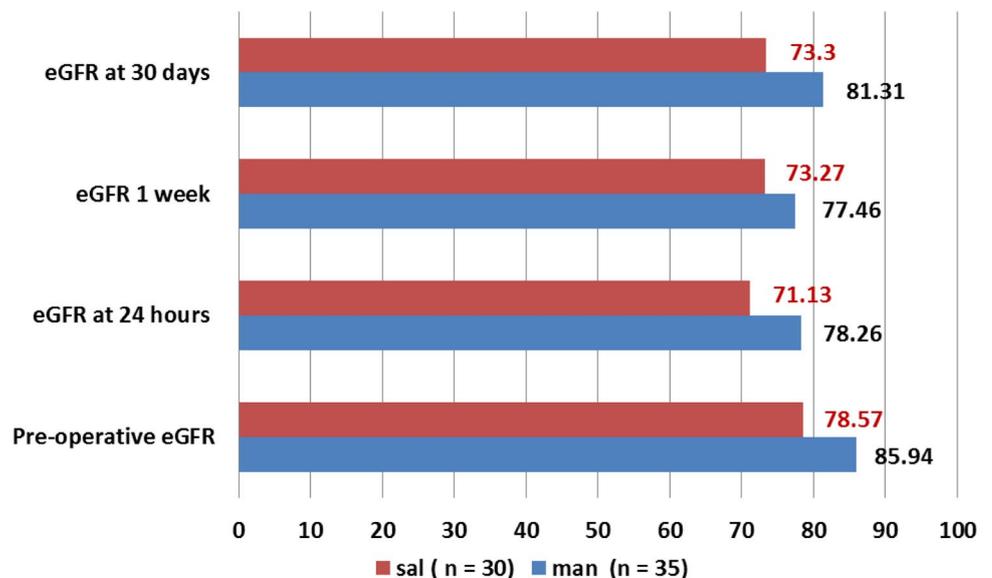
Table 1 Patient demographics

	Mannitol (n = 35)	Saline (n = 30)	p value
Age	60.8 ± 11.4 (32.9–81.0)	57.8 ± 10.9 (30.1–82.2)	0.2752
Gender (male)	19 (54.3%)	17 (56.7%)	0.8473
BMI	30.4 ± 6.32 (16.8–46.02)	34.5 ± 7.53 (20.2–57.3)	0.0230
Comorbidities			
DM	10 (28.6%)	12 (40.0%)	0.3317
PAD	1 (2.9%)	2 (6.7%)	0.5913
Hypertension	21 (61.8%)	18 (62.1%)	0.9802
Hypercholesteremia	11 (31.4%)	12 (40.0%)	0.4712
Baseline mean serum creatinine	0.87 ± 0.27 (0.5–1.6)	0.95 ± 0.21 (0.4–1.2)	0.1983
Mean sys bp	92.3 ± 24.68 (53–137)	103.8 ± 20.08 (65–132)	0.0633
Kidney length (mm)	105.0 ± 10.4 (89–142)	105.4 ± 9.9 (84–118)	0.8709
Tumor size (mm)	29.6 ± 13.5 (3–69)	31.9 ± 13.5 (3–69)	0.5078
Blood loss	115.1 ± 101.6 (15–450)	181.7 ± 160.9 (50–750)	0.0565
Total clamp time (min)	10.7 ± 4.75 (0–17.57)	11.2 ± 2.8 (6.01–16.57)	0.6211
Total neph score	6.08 ± 1.85 (4–10)	6.27 ± 1.8 (4–9)	0.6921
ASA score			
ASA ≤ 2	2 (5.7%)	1 (3.3%)	0.4266
ASA 3	30 (85.7%)	29 (96.7%)	
ASA ≥ 4	3 (8.6%)	0	

Table 2 Outcome variables (creatinine and eGFR)

	Mannitol (n = 35)	Saline (n = 30)	p value
Preoperative eGFR	85.94 ± 26.2 (42–138)	78.57 ± 31.02 (44–170)	0.3026
eGFR at 24 h	78.26 ± 26.4 (45–148)	71.13 ± 26.4 (34–171)	0.2820
eGFR percent change 24 h	− 6.34 ± 22.7 (− 58.5 to 39.2)	− 5.3 ± 29.6 (− 54.8 to 122.1)	0.8731
eGFR 1 week	77.46 ± 29.3 (22–162)	73.27 ± 24.2 (34–132)	0.5363
eGFR percent change 1 week	− 8.83 ± 23.6 (− 60.7 to 60.4)	− 6.92 ± 37.6 (− 54.8 to 122.1)	0.3889
eGFR at 30 days	81.31 ± 21.8 (35–124)	73.3 ± 24.9 (38.0–138.0)	0.1718
eGFR percent change 30 days	− 3.56 ± 14.5 (− 33.3 to 28.92)	− 4.18 ± 19.9 (− 47.6 to 71.4)	0.8843

Fig. 1 Mean eGFR levels of robotic partial nephrectomies



traditionally for improving outcomes in renal transplant patients based on previous studies. Mannitol is found to decrease reperfusion injury by acting as scavengers for free radicals, as well as working as a diuretic agent [4, 12, 13].

Despite its routine use in renal sparing surgeries, use of mannitol is not without risks. Acute renal injury was documented on several studies, mostly from high-dose mannitol use in a renal transplant patient in attempt to induce osmotic diuresis [7]. Furthermore, to this date, no standard guidelines are available to guide urologists on what dose will be optimal for renoprotection due to paucity of high-level evidence of mannitol use in partial nephrectomies. When urologists were polled regarding their mannitol usage practice during partial nephrectomy, great variability was found throughout the world. The two most common dosages used by urologists were 12.5 g (30%) and 25 g (49%) [6]. Based on variability and lack of standardization, 12 g was used in our study.

With the advanced technologies available including robotic surgery in addition to increasingly smaller renal masses being detected due to increased use of CT scans, efficient and effective partial nephrectomies with minimal warm ischemia are being performed. Faria et al. [8] found that warm ischemia time has decreased almost minutes in RALPN compared to laparoscopic approach and by approximately 4.5 min to the open approach. With the short warm ischemia time that is possible during robot use, we hypothesized that the routine use of mannitol in preserving renal function during partial nephrectomies would have minimal effect.

Although not isolated to a robotic cohort only, a retrospective review of 10 years of data by Cooper et al. showed that mannitol did not demonstrate renoprotective effects at 6 months on 476 patients that was done with both an open and with a minimally invasive surgical approach [11].

A recent publication from Memorial Sloan Kettering on mannitol use in partial nephrectomies supports our findings at 6-month follow-up [10]. Unlike our study, MSK study had open as well as laparoscopic cohorts and was not a single surgeon study. When compared to the robotic cohort only, the results were equal to our findings. With our homogeneous cohort, we are able to confirm data that is more representative of contemporary community practice using the RALPN. Our study is unique and is the first published study looking specific into robotic use in small renal mass partial nephrectomies as well as being a single surgeon study that decreases variability in surgical technique which could affect the outcome.

Limitations to our study include a small cohort, short term follow-up, and the exclusion of patients with decreased GFR in whom nephron sparing is likely to be even more important than someone with a normal GFR. We are currently enrolling more patients for further analysis to

strengthen our study. Additionally, we will be studying the effect of mannitol in patients with a lower GFR to evaluate any relationship in that cohort.

Conclusions

After prospective analysis of the change in post-operative renal function of randomized groups who received 12 g of mannitol following RALPN, we determined that infusion of mannitol does not provide significant improvement of maintenance of renal function after RALPN. Based on our results, we recommend discontinuing routine use of mannitol during RALPN.

Compliance with ethical standards

Conflict of interest Authors Kellen Choi, Sharon Hill, Stephen Phillips, Nathan Hale, and Samuel Deem declare that they have no conflict of interest.

Informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki declaration of 1975, as revised in 2000 [5]. Informed consent was obtained from all patients for being included in the study.

References

1. Cairns P (2010) *Cancer Biomark* 9(1–6):461–473. <https://doi.org/10.3233/CBM-2011-0176>
2. <https://www.cancer.org/cancer/kidney-cancer/about/key-statistics.html>. Accessed 11 July 2017
3. Chow W, Devesa SS, Warren JL et al (1999) Rising incidence of renal cell carcinoma in the United States. *JAMA* 281:1628
4. Nicholas E, Power AC, Maschino et al (2012) Intraoperative mannitol use does not improve long-term renal function outcomes after minimally invasive partial nephrectomy. *Urology* 79(4):821–825
5. Volpe A, Cadeddu JA et al (2011) Contemporary management of small renal masses. *Eur Urol* 60(3):501–515
6. Cosentino M, Breda A et al (2012) The use of mannitol in partial and live donor nephrectomy: an international survey. *World J Urol* 31:977–982
7. Visweswaran P, Massin EK, Dubose TD Jr (1997) Mannitol-induced acute renal failure. *J Am Soc Nephrol* 8(6):1028–1033
8. Gelman S (1996) Does mannitol save the kidney? *Anesth Analg* 82(5):899–901
9. Hemmelgarn BR et al (2010) Relation between kidney function, proteinuria, and adverse outcomes. *JAMA* 303(5):423
10. Spaliviero M, Power NE, Murray KS et al (2018) Intravenous mannitol versus placebo during partial nephrectomy in patients with normal kidney function: a double-blind, clinically-integrated, randomized trial. *Eur Urol* 73:53–59
11. Cooper CA, Shum CF, Bahler CD, Sundaram CP (2017) Intraoperative mannitol not essential during partial nephrectomy. *J Endourol*. <https://doi.org/10.1089/end.2017.0415>. (Epub ahead of print)

12. Joannidis M, Druml W, Forni LG et al (2010) Prevention of acute kidney injury and protection of renal function in the intensive care unit. Expert opinion of the Working Group for Nephrology, ESICM. *Intensive Care Med* 36:392
13. Collins GM, Green RD, Boyer D, Halasz NA (1980) Protection of kidneys from warm ischemic injury. Dosage and timing of mannitol administration. *Transplantation* 29:83–84