Published in final edited form as:

Eur Urol Focus. 2019 November ; 5(6): 977–979. doi:10.1016/j.euf.2019.04.003.

Phase III Trial of Intravenous Mannitol Versus Placebo During Nephron-sparing Surgery: Post Hoc Analysis of 3-yr Outcomes

Nathan C. Wong^a, Ricardo G. Alvim^a, Daniel D. Sjoberg^b, Roman Shingarev^c, Nicholas E. Power^d, Massimiliano Spaliviero^e, Katie S. Murray^f, Nicole E. Benfante^g, A. Ari Hakimi^a, Paul Russo^a, Jonathan A. Coleman^{a,*}

^aUrology Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA

^bDepartment of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY, USA

^cRenal Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA

^dDivision of Urology, Western University, London, ON, Canada

^eStony Brook Medicine, SUNY at Stony Brook, Stony Brook, NY, USA

^fDepartment of Surgery, Division of Urology, University of Missouri, Columbia, MO, USA

^gSloan Kettering Institute, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Abstract

Our recently reported phase III trial demonstrated that patients undergoing nephron-sparing surgery (NSS) with an estimated glomerular filtration rate (eGFR) of ≥ 45 ml/min/1.73 m² who received mannitol had no improvement in renal function at 6 mo compared with those who received placebo. Some authors have suggested that benefit is restricted to subgroups, such as those with comorbidities. We assessed whether preoperative eGFR, or other patient and surgical

*Corresponding author. Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, USA. Tel. +1 646 422 4432; Fax: +1 212 452 3323. colemanj@mskcc.org (J.A. Coleman).

Author contributions: Jonathan A. Coleman had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Wong, Coleman.

Acquisition of data: Wong, Alvim, Sjoberg, Benfante.

Analysis and interpretation of data: Wong, Alvim, Sjoberg, Shingarev, Power, Spaliviero, Murray, Hakimi, Russo, Coleman.

Drafting of the manuscript: Wong, Alvim, Sjoberg.

Critical revision of the manuscript for important intellectual content: Wong, Alvim, Sjoberg, Shingarev, Power, Spaliviero, Murray, Benfante, Hakimi, Russo, Coleman.

Statistical analysis: Sjoberg, Benfante.

Obtaining funding: Hakimi, Russo, Coleman.

Administrative, technical, or material support: Benfante.

Supervision: Hakimi, Russo, Coleman.

Other: None.

Financial disclosures: None.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

factors modified the effect of mannitol on postoperative outcomes at 6 mo and with extended follow-up. We also assessed whether mannitol was associated with differences in long-term GFR years after surgery. No significant difference between the mannitol or placebo groups (mean eGFR difference: 1.4; 95% confidence interval: -2.6, 5.3; $p = 0.5$) was found in the 134 patients with known eGFR at 3 yr after NSS. At both 6 mo and 3 yr, the effect of mannitol was not significantly modified by patient or surgical factors including preoperative eGFR. In summary, we validated our original trial conclusions by finding that intraoperative use of mannitol does not improve either short- or long-term renal function in patients undergoing NSS. Specifically, there is no evidence that comorbidities, including lower preoperative eGFR, modify the effect of mannitol.

Patient summary:

Use of mannitol at the time of partial nephrectomy does not improve either short- or long-term renal function even in patients with comorbidities, including lower preoperative renal function. The routine use of intraoperative mannitol should be discontinued.

Keywords

Mannitol; Nephron-sparing surgery; Partial nephrectomy; Renal function

The benefit of intraoperative mannitol in patients undergoing nephron-sparing surgery (NSS) has been of recent clinical interest and investigation. Following a retrospective analysis at our center that showed no benefit of mannitol in renal function at 6 mo, we performed a prospective, randomized, placebo-controlled, double-blind, clinically integrated study to evaluate the role of mannitol at the time of NSS [1,2]. The trial design has been described previously [2]. We recruited 199 patients between July 2012 and July 2015. Eligible patients had a renal mass, were 18 yr old, were medically cleared for NSS during which renal ischemia was anticipated, and had a preoperative estimated glomerular filtration rate (eGFR) of 45 ml/min/1.73 m². Patients were randomized 1:1 using a secure computer system to receive mannitol or normal saline solution, stratified by preoperative eGFR (<60 vs 60 ml/min/1.73 m²) and surgical approach (open vs minimally invasive). The treatment arm received a standard dose of 12.5 g of mannitol (200 ml of 6.25% mannitol solution), infused intravenously over 5–10 min within 30 min prior to vascular occlusion of the renal artery. The 95% confidence interval (CI) for differences in eGFR at 6 mo following NSS excluded clinically relevant benefit, suggesting that the routine use of mannitol should be discontinued.

The study population was predominately healthy (Supplementary Table 1), and it was hypothesized that the benefit of mannitol in patients is restricted to patients with comorbidities, including lower preoperative eGFR [3–5]. For instance, Dalela et al [3] suggested that study patients were able to “withstand physiological perturbations during and after surgery” and recover their renal function regardless of the use of mannitol; clinical benefits of mannitol would be seen only in “sicker” patients with “the most to lose.” Others commented that the renal masses were small and ischemia times were short, theorizing that large complex tumors requiring longer ischemia times may benefit from the supposed protective effects of mannitol due to the greater number of nephrons lost. Here, we address

these issues with a post hoc analysis of trial data, including assessment of the long-term renal function outcomes at 3 yr after NSS. Our main objective was to determine whether any “at-risk” patient groups would benefit from the use of intraoperative mannitol.

We first sought to determine whether there were any differences in eGFR at long-term follow-up. Of the 199 randomized patients, the 134 (67%) with both preoperative and 3-yr (± 6 mo) postoperative eGFR available were included in the current analysis. We tested whether mannitol led to differences in 3-yr eGFR by analysis of covariance (ANCOVA), with baseline eGFR and surgical approach as covariates. Similar to the results of our original study, we found that the use of mannitol was not associated with eGFR changes at either 6 mo or 3 yr (mean 3-yr eGFR difference: 1.4; 95% CI -2.6, 5.3; $p = 0.5$; Table 1). The narrow CI suggests that any plausible effects of mannitol on long-term eGFR would not be clinically meaningful.

Next, we repeated the ANCOVA analysis including interaction terms to determine whether the effectiveness of mannitol on renal function differed by various patient and surgical characteristics, including preoperative eGFR, coronary artery disease, diabetes, tumor size, surgical approach, and ischemia time. Each characteristic was also included as a main effect in the model. A significant interaction would suggest that the effect of mannitol depended on the level of baseline characteristics. After performing such analyses using the 6-mo and 3-yr eGFR measurements, the effect of mannitol was not significantly modified by patient or surgical factors, including preoperative eGFR, coronary artery disease, diabetes, surgical approach, ischemia time, and tumor size at either time point (Fig. 1).

Although we did not observe any significant effect of preoperative eGFR on the usefulness of mannitol during NSS, the central estimates are informative. Mannitol was even less effective among patients with a lower preoperative eGFR (Fig. 1), providing evidence against the potential benefit of mannitol in patients with a lower preoperative eGFR. If mannitol was to be effective in this group, we should have instead observed at least a trend of more effectiveness in patients with a lower eGFR prior to surgery. Additionally, the central estimates show a slightly higher eGFR at 6 mo in mannitol-receiving patients with larger tumors and in those undergoing open surgery, but these trends were reversed at 3 yr follow-up. Owing to the observed reverse effects, the observed differences are likely due to random variation rather than a true effect.

In addition to our original study, two recent retrospective studies and another randomized trial found no benefit of mannitol use in patients undergoing NSS [1,6,7]. Omae et al [7] evaluated the role of mannitol in 55 patients with a solitary kidney undergoing open NSS. They found no significant differences in postoperative eGFR at any time point within 6 mo. A randomized controlled trial of 65 patients undergoing robotic NSS, which compared mannitol with normal saline, also showed no benefit in percent change in eGFR at 30 d [8].

The hypothesized benefits of mannitol in NSS have been extrapolated mainly from preclinical models and renal transplant literature, where the mechanisms of postsurgical renal dysfunction are more complex. However, evidence suggests that mannitol use offers no advantage to patients undergoing NSS when compared with standard fluid

hydration, including in specific subgroups, such as patients with a solitary kidney, large masses, anticipated long ischemia times, or a lower preoperative eGFR. Furthermore, renal physiology studies have suggested that a competitive mechanism from the increased metabolic burden of mannitol may in fact have a detrimental effect on renal function [9]. In our previous trial, we focused our evaluation on patients who were relatively healthy, with a low number of patients “at risk” for renal dysfunction. This limits direct application of our findings to patients outside of our initial study inclusion criteria. Despite this, we find no evidence that mannitol at the time of NSS improves either short- or long-term renal function, even in “at-risk” patients with comorbidities, including lower preoperative renal function. This validates our original trial conclusions that the routine use of mannitol should be discontinued.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding/Support and role of the sponsor: This research was supported by the Sidney Kimmel Center for Prostate and Urologic Cancers and funded in part through the NIH/NCI Cancer Center Support Grant P30 CA008748.

References

- [1]. Power NE, Maschino AC, Savage C, et al. Intraoperative mannitol use does not improve long-term renal function outcomes after minimally invasive partial nephrectomy. *Urology* 2012;79:821–5. [PubMed: 22469577]
- [2]. Spaliviero M, Power NE, Murray KS, et al. Intravenous mannitol versus placebo during partial nephrectomy in patients with normal kidney function: a double-blind, clinically-integrated, randomized trial. *Eur Urol* 2018;73:53–9. [PubMed: 28822586]
- [3]. Dalela D, Abdollah F, Rogers C. Re: Massimiliano Spaliviero, Nicholas E. Power, Katie S. Murray, et al. Intravenous mannitol versus placebo during partial nephrectomy in patients with normal kidney function: a double-blind, clinically-integrated, randomized trial. *Eur Urol* 2018;73:53–9. *Eur Urol* 2018;74:e48–9. [PubMed: 28822586]
- [4]. Laguna MP. Re: Intravenous mannitol versus placebo during partial nephrectomy in patients with normal kidney function: a double-blind, clinically-integrated, randomized trial. *J Urol* 2018;199:1108–9. [PubMed: 29677895]
- [5]. Shah PH, Leibovich BC, Lyon TD. Should urologists abandon the use of mannitol during partial nephrectomy? *Eur Urol* 2018;73:60–1. [PubMed: 28985968]
- [6]. Cooper CA, Shum CF, Bahler CD, Sundaram CP. Intraoperative mannitol not essential during partial nephrectomy. *J Endourol* 2018;32:354–8. [PubMed: 29216760]
- [7]. Omae K, Kondo T, Takagi T, et al. Mannitol has no impact on renal function after open partial nephrectomy in solitary kidneys. *Int J Urol* 2014;21:200–3. [PubMed: 23819791]
- [8]. Choi K, Hill S, Hale N, Phillips S, Deem S. Intraoperative mannitol during robotic-assisted-laparoscopic partial nephrectomy. *J Robot Surg*. In press. 10.1007/s11701-018-0868-4
- [9]. Gelman S. Does mannitol save the kidney? *Anesth Analg* 1996;82:899–901. [PubMed: 8610895]

1A

1B

Fig. 1 –.

Effect of mannitol on postoperative estimated glomerular rates (at 6 mo and 3 yr) stratified by (A) continuous variables (clamp time, maximum tumor diameter, and preoperative eGFR) and (B) categorical variables (presence of coronary artery disease, diabetes, and surgical approach).

eGFR = estimated glomerular filtration rate; GFR = glomerular filtration rate; Sx = surgery.

Table 1 –

Postoperative mean estimated glomerular filtration rates in patients who received mannitol versus placebo

	<i>N</i>	Mannitol	Placebo	Difference	95% CI	<i>p</i> value
6-mo eGFR	178	78 (20)	80 (18)	–0.2	–3.5, 3.1	>0.9
3-yr eGFR	134	77 (20)	79 (16)	1.4	–2.6, 5.3	0.5

CI = confidence interval; eGFR = estimated glomerular filtration rate.