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Intravenous Mannitol Versus Placebo During Partial Nephrectomy in Patients with Normal Kidney Function: A Double-blind, Clinically-integrated, Randomized Trial

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Abstract

Background: Mannitol is currently used as a renal protective agent to mitigate the effects of renal ischemia during nephron-sparing surgery (NSS). This routine practice lacks rigorous methodological study.

Objective: To assess the effect on renal function outcomes after surgery of mannitol infusion prior to renal ischemia during NSS.

Design, setting, participants: This prospective, randomized, placebo-controlled, double-blind trial included 199 patients with a preoperative estimated glomerular filtration rate (eGFR) >45 ml/min/1.73m² scheduled for NSS; the trial was conducted between July 2012 and July 2015.

Intervention: Patients undergoing NSS were randomized to receive mannitol (12.5 g) or placebo intravenously within 30 min prior to renal vascular clamping.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.eururo.2017.07.038>.

Outcome measurements and statistical analysis: The primary outcome was the difference in eGFR (renal function) between the two groups at 6 mo following surgery assessed with an analysis of covariance model using preoperative eGFR, treatment group, and surgical approach as covariates.

Results and limitations: At baseline, the median age of the patients was 58 yr, and the median eGFR was 88 ml/min/1.73m². Comparing placebo with mannitol infusion, the adjusted difference of 0.2 eGFR units at 6 mo was not significant ($p = 0.9$), with the upper bound of the 95% confidence interval (−3.1 to 3.5) excluding a clinically relevant effect of mannitol. Limitations include evaluation of a single mannitol dose and patients all had excellent preoperative renal function.

Conclusions: Intraoperative 12.5 g mannitol infusion during NSS has no demonstrable clinical benefit when compared with standardized fluid hydration in patients with normal preoperative renal function, and its use in this setting is not warranted.

Patient summary: In this randomized trial, patients with normal kidney function who received mannitol during surgery to remove part of their kidney had no better kidney function 6 mo after surgery than those who did not receive mannitol. We conclude that this routine practice should be discontinued.

Keywords

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

1. Introduction

A key clinical outcome of nephron-sparing surgery (NSS) is the detrimental effect of surgery on renal function, particularly when temporary renal vascular clamping is applied to optimize visualization for excision, repair, and hemostasis [1]. Modifiable factors employed to minimize detrimental effects include the utilization of cold ischemia, limiting the duration of renal artery occlusion, and intraoperative use of renal protective agents prior to renal ischemia.

Mannitol is an osmotic diuretic used during NSS to mitigate the effects of ischemic renal injury. Cited evidence has been drawn from clinical experience and preclinical animal studies [1]. Associated prostaglandin-mediated vasodilatory effects, the release of atrial natriuretic peptide, or a combination of both mechanisms have been suggested as factors that increase renal blood flow [2,3]. Others include free-radical scavenging, reduction of renin production, and expansion of intravascular volume [4].

To our knowledge, no randomized trial exists that supports the use of mannitol during NSS. A recent randomized trial presented at the American Urological Association 2017 meeting confirms our findings in minimally invasive NSS [5]. On the contrary, renal physiology studies indicate that a competitive mechanism from increased metabolic demand might actually have a detrimental effect on renal function [6].

Comparative retrospective data has raised further questions about the clinical value of mannitol during NSS. Functional outcomes measured by estimated glomerular filtration rate (eGFR) within 6 mo after surgery were no different between 164 surgical patients who received mannitol versus 121 who did not [7]. Based on this data, we conducted a randomized controlled trial to compare the effects of mannitol versus placebo on postoperative kidney function in patients undergoing NSS for renal cell cancer.

2. Materials and methods

2.1. Trial design and participants

The trial was a prospective, randomized, placebo-controlled, double-blind, clinically integrated trial. Patients were recruited between July 2012 and July 2015. Approximately 46% of eligible patients consented (Fig. 1).

Eligible patients had a renal mass, were 18 yr old, medically cleared for NSS during which renal ischemia was anticipated, and had a pre-operative eGFR ≥ 45 ml/min/1.73 m² (Chronic Kidney Disease Epidemiology Collaboration). NSS was performed using an open or minimally invasive approach. Exclusion criteria included allergy to mannitol, severe renal function impairment (stage 3B) defined as eGFR < 45 ml/min/1.73 m², or multiple surgical procedures combined with NSS. Randomization was stratified by preoperative eGFR (< 60 vs ≥ 60 ml/min/1.73 m²) and surgical approach (open vs minimally invasive), and patients were assigned in a 1:1 ratio to receive mannitol or normal saline. Randomization occurred immediately after consent was obtained preoperatively and was performed using permuted blocks of random length by the independent Clinical Research Database office, which ensured concealment of allocation with a password-protected database. Assignments were communicated via telephone or encrypted email to the pharmacy. With the exception of the hospital pharmacists who dispensed the study drugs, all participants were masked to the treatment assignments.

The protocol was approved by the Memorial Sloan Kettering Institutional Review Board. All patients provided written informed consent before enrollment and surgery. The formal trial protocol can be found in the Supplementary data.

2.2. Interventions and follow-up

All patients underwent routine history and physical examination, as well as baseline renal scintigraphy scan within 6 mo of surgery, an abdominal and pelvic computed tomography scan and/or a renal ultrasound within 2 mo of surgery, chest X-ray or computed tomography within 30 d of surgery, and preoperative laboratory investigations, including baseline eGFR.

The choice of approach and use of renal hypothermia during NSS was at the discretion of the patient and treating physician. Selective occlusion of multiple primary renal arteries, when present, or nonclamping of the artery, was performed at the surgeon's discretion and recorded. Routine clamping of the renal vein(s) was not performed ($n = 2$, both in the mannitol arm).

The intraoperative fluid management was standardized to maintain a minimum systolic blood pressure of 90–100 mmHg and a minimum urine output of 0.5 ml/kg/h. This included intravenous hydration at a target infusion rate of 10 ± 1 ml/kg over the 1st h of surgery and of 6 ± 1 ml/kg thereafter. Intraoperative hypotension (systolic blood pressure < 90 mmHg) or urine output < 0.5 ml/kg/h were treated with 250-ml intravenous boluses of Normosol. Hypotension refractory to intravenous fluid boluses was treated with small doses of intravenous phenylephrine or ephedrine or neostigmine or combinations thereof. The protocol allowed for replacement of surgical blood loss on a volume basis ml per ml using colloids, such as albumin or 6% hetastarch solution, or packed red blood cell units transfused.

The treatment arm received a standard dose of 12.5 g of mannitol (200 ml of a 6.25% mannitol solution), completely infused intravenously over 5–10 min within 30 min prior to vascular occlusion of the renal artery. The placebo arm received 200 ml of normal saline solution.

Follow-up assessments included serum creatinine and eGFR measurements on postoperative d 1 and 2, at 6 wk, and 6 mo; and a renal scintigraphy scan at 6 mo.

Secondary endpoints included the determination of differences between the arms in eGFR at 6 wk (± 2 wk), a postoperative radionuclear scintigraphy renal scan at 6 mo (± 1 mo), rates of grade 3–5 complications within 30 d of surgery, estimated blood loss, and ischemia time.

2.3. Adverse events

Perioperative complications were defined as any complication grade ≥ 2 in the Memorial Sloan Kettering-modified Clavien-Dindo grading system that occurred intraoperatively and within 30 d postoperatively. Intraoperative complications were defined as any complication of grade ≥ 2 related to either surgical or clinical factors during the procedure. Immediate perioperative morbidity was defined as any complication grade ≥ 2 that occurred during the initial hospital stay.

2.4. Sample size

The primary objective was to determine the difference in eGFR between the mannitol group and the placebo group 6 mo after NSS. Based on historical data [7], the expected mean eGFR at 6 mo after NSS in patients who did not receive mannitol was 60 ml/min/1.73 m². The observed correlation between preoperative eGFR and 6-mo postoperative eGFR was 0.6. The standard deviation was 14.4 ml/min/1.73 m², and the 75th percentile of the standard deviation estimated using bootstrap methods was 14.9 ml/min/1.73 m². This inflated standard deviation was used for the sample size calculation as a conservative measure to reduce the likelihood of underpowering. To detect a minimal clinically significant difference of six units of eGFR, a trial with an α of 5%, a power of 90%, and a planned interim analysis for efficacy required 88 patients per treatment arm. Sample size was expanded to 105 patients per treatment arm to account for loss to follow-up.

2.5. Statistical analysis

The difference in eGFR at 6 wk and 6 mo between the two groups was assessed by analysis of covariance (ANCOVA) with eGFR after surgery as the outcome, and preoperative eGFR, randomization treatment group, and surgical approach as covariates. A threshold of six units of eGFR was used to define clinical significance. Two-tailed *p* value and a 95% confidence interval (CI) for the difference between groups were determined. In accordance with the study protocol, a linearly interpolated 6-mo eGFR was calculated for patients who missed an eGFR measurement between 4 mo and 8 mo after surgery, but who had eGFR measured at 3 mo and between 8 mo and 12 mo ($n = 15$).

The ANCOVA model was also used to compare baseline and 6-mo nuclear renal scintigraphy differences, estimated blood loss, and ischemia time. The ANCOVA model included treatment, baseline eGFR, and type of surgery as covariates. The renal scintigraphy model also included baseline renal scintigraphy measurements. Owing to the paucity of 90-d grade 3–5 complications occurring during the study ($n = 15$ grade 3–5 complications), the Fisher's exact test was used to assess the differences between the treatment groups.

The primary analysis was conducted according to intention to treat. Analyses of the main and secondary endpoints were also repeated according to the actual treatment received. O'Brien-Fleming stopping boundaries and a significance level of 0.0031 were utilized for the interim analysis [8]. All analyses were conducted using Stata 13.0 (StataCorp LP, College Station, TX, USA).

3. Results

Overall, 210 patients were enrolled in the trial. Of these, 105 were assigned to each treatment arm. Five patients in the placebo arm and four patients in the mannitol arm withdrew consent prior to surgery and were excluded from all analyses. Two patients in the placebo arm had their surgery cancelled and they were excluded as well. NSS was converted to radical nephrectomy in one patient in each arm, and one patient in the mannitol arm never received the study drug during NSS. These three patients were included in the analyses according to the intent-to-treat principle; thus, 98 and 101 patients were included in the placebo and mannitol arms, respectively (Fig. 1). Baseline characteristics of the two groups were similar (Table 1). None of the patients received intraoperative intravenous diuretics (ie, furosemide).

3.1. Renal function and adverse event outcomes

Renal function outcomes are shown in Table 2 and Figure 2. Of the 199 patients studied, 178 (91 in the placebo arm and 87 in the mannitol arm) had complete 6-mo eGFR data and were included in the primary analysis. After adjusting for preoperative eGFR and surgical technique, the difference in 6-mo eGFR was 0.2 (95% CI: -3.1 to 3.5 , $p = 0.9$). A total of 180 patients (91 in the placebo arm and 89 in the mannitol arm) had complete 6-wk eGFR data and were included in the 6-wk comparison. Similar to the 6-mo analysis, no significant difference in eGFR between the two arms was detected (adjusted difference: -2.6 , 95% CI: -5.8 to 0.7 , $p = 0.12$).

No significant differences were observed on 6-mo renal unit % split function radionuclear scintigraphy scans (adjusted difference: -1.7 , 95% CI: -3.8 to 0.4 , $p = 0.11$). Overall, 15 (7.5%) grade 3–5 complications were observed in the trial, and no difference was detected between the study arms (difference: 3.2%, 95% CI: -4.1% to 11% , $p = 0.4$). Estimated blood loss and renal ischemia time were also similar ($p = 0.2$ and $p = 0.7$, respectively; Table 2.)

We did not find that the effect of mannitol on postoperative eGFR differed by baseline eGFR (6-mo eGFR $p = 0.9$; 6-wk eGFR, $p = 1$) or by type of surgery (6-mo eGFR $p = 0.2$; 6-wk eGFR, $p = 0.5$).

Post-hoc analysis was completed to determine if there was interaction between mannitol and clamp time and it was not significant ($p = 0.09$).

4. Discussion

The primary aim of this study was to assess the impact on renal function of intravenous mannitol to determine its role as an agent that protects against the effects of transient renal ischemia during NSS. The results of our study show that mannitol has no clinically measurable effect on renal function recovery after NSS in patients with adequate preoperative renal function. Indeed, the upper bound of the 95% CI for the difference between study groups excluded the prespecified minimum clinically significant difference. We can thus conclude that mannitol should not be used in NSS in this clinical context.

Earlier publications of several well-conducted animal studies have been used to support the use of mannitol [1]. Green et al [9] used acute and chronic models to test the administration of medications on the recovery of rabbit kidneys from the effects unilateral normothermic renal ischemia after 1 h of renal vascular occlusion. Only propranolol and the diuretics mannitol and furosemide showed beneficial effect. A follow-up study determined that 0.25 g/kg of mannitol administered 15 min before warm renal ischemia was beneficial [10]. The standard dose of 12.5 g of intravenous mannitol administered during NSS resulted from these studies [9,10]. Considering higher doses of mannitol, a prospective randomized trial on 50 recipients of cadaveric donor renal transplant comparing the administration of either 50 g of intravenous mannitol or saline infusion prior to graft revascularization showed a significantly decreased incidence of postoperative ATN in the mannitol group, no impact on the 3-mo eGFR was detected [11].

To date, the use of intravenous mannitol during NSS has been part of surgical practice largely due to its legacy effect, and despite the potential risks. Detrimental renal effects investigated by Gelman [6] identified disproportionate shifts of the renal blood flow received by the renal cortex (94%) compared with the renal medulla (6%). By selectively increasing renal cortical blood flow, filtration rate, and resulting solute load, mannitol can artificially reduce medullary blood flow while simultaneously increasing metabolic demand, further compromising renal tissue [6]. These changes may potentiate the effects of ischemia by decreasing the medullary protective mechanisms that occur during oliguric renal failure, including reduction of renal blood flow, thereby decreasing GFR and metabolic load for solute reabsorption [12].

Recent studies, including a meta-analysis of renal protective agents for contrast-induced nephropathy and Cochrane analysis of the use of perioperative renal protective agents, found no benefit from the use of mannitol in preserving renal function in these settings [13,14].

A retrospective review at our institution evaluated the use of intravenous mannitol during minimally invasive NSS and found no evidence of clinically meaningful benefit in patients who received mannitol intraoperatively [7]. eGFR recovery models were similar between mannitol and nonmannitol groups at any point in the postoperative period. Several factors affected the ability of this retrospective study to definitively evaluate the use of mannitol as a protective agent during renal ischemia.

Recently, Omae et al [15] reported their retrospective experience on the effect of mannitol in 55 patients with a renal mass in a solitary kidney treated with open NSS. Mannitol was given within 15 min before clamping the renal artery, and ice-slush cold ischemia used. The mean postoperative eGFR at 1 d, 1 mo, 3 mo, and 6 mo postoperatively was similar in the 20 patients who received mannitol and the 35 patients who did not. On multivariate analysis, only ischemia time was associated with changes in postoperative eGFR.

An international survey on the use of mannitol in partial and living-donor nephrectomy in 92 high-volume urologic centers reported the use of mannitol in 79% and 65% of centers performing NSS and living-donor nephrectomy, respectively, with an 83% overall rate of utilization of mannitol [16]. In NSS, infused mannitol varied between 12.5 g in 30% of cases, 25 g in 49%, and other dosages in 22%. This high degree of nonstandardized, variable application in clinical practice combined with a lack of supporting clinical evidence is a cautionary tale.

The strengths of our study include (1) the randomized, double-blind, placebo-controlled design, (2) standardized perioperative protocols, (3) robust follow-up at all study visits, and (4) the comprehensive renal function evaluation. Our finding provides the foundation for a change in clinical practice, supporting standardized fluid management without mannitol during NSS as the standard of care.

The limitations of our study include evaluating a single dosage regimen of mannitol when results from a recent survey suggest that 25 g is the most common practice. Additionally, most patients had adequate preoperative renal function and therefore the effect of mannitol in patients with poor baseline kidney function is unknown. Pre-enrolment selection bias is also a potential limitation considering the number of patients who were not approached for the study.

5. Conclusions

Intravenous mannitol infusion during NSS does not lead to clinically relevant improvement in renal function outcomes, and its use in patients with adequate renal function should be discontinued.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1 –.

Flow diagram for enrollment and randomization of trial.

MD = medical doctor; preop = preoperative; RCC = renal cell carcinoma.

Fig. 2 –.

Estimated glomerular filtration rate (eGFR) over the study period by treatment group. Small gold dots represent the observed eGFR in patients enrolled in the mannitol arm; small blue dots represent the observed eGFR in patients randomized to placebo. Large dots represent the treatment group means.

Table 1 –

Characteristics of participants

	Statistic	Placebo (N = 98; 49%)	Mannitol (N = 101; 51%)
Age at surgery (yr)	Median (IQR)	56 (48, 63)	60 (50, 66)
Sex			
Female	n (%)	37 (38)	36 (36)
Male	n (%)	61 (62)	65 (64)
Race			
White	n (%)	80 (82)	81 (80)
Black	n (%)	10 (10)	5 (5.0)
Asian	n (%)	5 (5.1)	5 (5.0)
Other	n (%)	1 (1.0)	4 (4.0)
Unknown	n (%)	2 (2.0)	6 (5.9)
Minimally invasive procedure	n (%)	41 (42)	41 (41)
Clamping	n (%)	97 (99)	100 (99)
Cold ischemia used	n (%)	54 (56)	58 (59)
Clamp time cold ischemia (min)	Median (IQR)	27 (24, 35)	30 (23, 35)
Clamp time warm ischemia (min)	Median (IQR)	19 (16, 24)	20 (16, 25)
BMI	Median (IQR)	30 (27, 34)	30 (27, 34)
Baseline serum hemoglobin	Median (IQR)	13.7 (12.8, 14.7)	13.8 (12.9, 14.8)
Baseline serum albumin (N= 148)	Median (IQR)	4.4 (4.2, 4.6)	4.4 (4.3, 4.6)
ASA score			
1	n (%)	2 (2.0)	1 (1.0)
2	n (%)	34 (35)	39 (39)
3	n (%)	60 (61)	57 (56)
4	n (%)	2 (2.0)	4 (4.0)
Karnofsky Scale at baseline			
60	n (%)	1 (1.0)	0 (0)
70	n (%)	1 (1.0)	0 (0)
80	n (%)	2 (2.0)	4 (4.0)
90	n (%)	13 (13)	16 (16)

	Statistic	Placebo (N = 98; 49%)	Mannitol (N = 101; 51%)
100	n (%)	80 (82)	81 (80)
Unknown	n (%)	1 (1.0)	0 (0)
Pathologic T stage			
T0	n (%)	8 (8.2)	9 (8.9)
T1	n (%)	0 (0)	2 (2.0)
T1A	n (%)	61 (62)	68 (67)
T1B	n (%)	19 (19)	13 (13)
T2B	n (%)	0 (0)	1 (1.0)
T3A	n (%)	9 (9.2)	8 (7.9)
T3B	n (%)	1 (1.0)	0 (0)
Histology			
Angiomyolipoma	n (%)	5 (5.1)	3 (3.0)
Chromophobe	n (%)	7 (7.1)	10 (10)
Clear cell papillary	n (%)	2 (2.0)	1 (1.0)
Conventional clear cell	n (%)	58 (59)	56 (55)
Cystic lesions	n (%)	0 (0)	2 (2.0)
Metanephric adenoma	n (%)	0 (0)	1 (1.0)
Oncocytoma	n (%)	7 (7.1)	6 (5.9)
Other	n (%)	4 (4.1)	4 (4.0)
Papillary	n (%)	15 (15)	18 (18)
Charlson Comorbidity Index			
0	n (%)	66 (67)	71 (70)
1	n (%)	20 (20)	12 (12)
2	n (%)	10 (10)	12 (12)
3	n (%)	2 (2.0)	5 (5.0)
5	n (%)	0 (0)	1 (1.0)
Intraoperative urine output, ml (N = 193)	Median (IQR)	175 (130, 250)	200 (120, 280)
Intraoperative IV fluid intake, ml (N = 192)	Median (IQR)	2300 (1900, 2900)	2300 (2000, 2850)
RENAL Nephrometry Score			
4	n (%)	3 (3.1)	6 (5.9)
5	n (%)	4 (4.1)	2 (2.0)

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	Statistic	Placebo (N = 98; 49%)	Mannitol (N = 101; 51%)
6	n (%)	10 (10)	8 (7.9)
7	n (%)	15 (15)	12 (12)
8	n (%)	14 (14)	12 (12)
9	n (%)	6 (6.1)	6 (5.9)
10	n (%)	8 (8.2)	11 (11)
11	n (%)	2 (2.0)	1 (1.0)
Unknown	n (%)	36 (37)	43 (43)
Maximal tumor diameter, cm (N = 192)	Median (IQR)	3.0 (2.3, 4.0)	2.7 (1.9, 4.0)
Preoperative eGFR	Median (IQR)	89 (78, 100)	86 (71, 99)
Preoperative eGFR <60	n (%)	5 (5.1%)	13 (13%)
Scan result preop for side of tumor (N = 195)	Median (IQR)	49 (47, 52)	50 (47, 53)

ASA = American Society of Anesthesiologists; BMI = body mass index; eGFR = estimated glomerular filtration rate; IQR = interquartile range; IV = intravenous; preop = preoperative.

Table 2 –

Primary and secondary endpoint outcomes

	Placebo (<i>n</i> = 98)	Mannitol (<i>n</i> = 101)	Difference	95% CI	<i>p</i> value
6-mo postoperative eGFR (<i>n</i> = 178)					0.9
eGFR ml/min/1.73m ² ^a	80 (18)	78 (20)	0.2	-3.1 to 3.5	
% change from preoperative eGFR	-8.4 (12)	-8.5 (14)	0.1	-3.8 to 4.0	
eGFR <60 ml/min/1.73m ²	12 (13%)	18 (21%)	-8%	-18% to 3.5%	
6-wk postoperative eGFR (<i>n</i> = 180)					0.12
eGFR ml/min/1.73m ² ^a	80 (19)	79 (20)	-2.6	-5.8 to 0.7	
% change from preoperative eGFR	-9.4 (14)	-6.2 (13)	-3.2	-7.1 to 0.7	
eGFR <60 ml/min/1.73m ²	13 (14%)	19 (21%)	-7%	-18% to 4.1%	
6-mo renal scan % split function ^a (<i>n</i> = 161)	42 (8)	44 (8)	-1.7	-3.8 to 0.4	0.11
Grade 3–5 complications (<i>n</i> = 199)	9 (9.2%)	6 (5.9%)	3.2%	-4.1% to 11%	0.4
Estimated blood loss (ml)	235 (218)	284 (297)	-47	-119, 26	0.2
Clamping time (min)	27 (13)	27 (12)	-0.7	-3.9, 2.6	0.7

Statistics presented in the first two columns indicate the mean (standard deviation).

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

^aIndividual renal unit where nephron sparing surgery was completed. Difference adjusted for preoperative eGFR and surgical approach. The 6-mo renal scan model was also adjusted for baseline renal scan (% split function for individual renal units).