Mannitol for the Prevention of Perioperative Acute Kidney Injury – A Systematic Review

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Abstract

Postoperative acute kidney injury (AKI) is a frequent perioperative complication that negatively affects morbidity and mortality. Mannitol is frequently used perioperatively for renal protection, although evidence for its use is ambiguous. We conducted a systematic review to clarify whether there is evidence supporting perioperative mannitol administration for the prevention of postoperative AKI.

A systematic literature search was performed in Medline/ Pubmed, Embase, the Cochrane Library, Clinical Trials registry, and the Cochrane Central Register of Controlled Trials (CENTRAL). Eligibility criteria were (1) population: studies involving adult patients undergoing surgery or a related intervention; (2) intervention: i.v. mannitol administered in either the pre-operative or intra-operative period with comparison to control subjects; and (3) predefined outcomes: postoperative AKI or respective renal endpoints/surrogates.

We identified 1,538 articles published between January 1990 and October 2018. After checking for eligibility, 22 studies including 17 prospective and/or randomized controlled trials and 5 retrospective studies were included. The investigations involved various fields of surgery, such as aortic surgery, cardiac surgery with cardiopulmonary bypass, and urological procedures including partial nephrectomy. Significant heterogeneity, limited sample size, and mostly short follow-up periods were noted.

Given available evidence, the perioperative use of mannitol to prevent AKI cannot be considered an evidence-based intervention in cardiac surgery, partial nephrectomy, and/or other major surgery. Further research is required with a focus on patients at high risk for postoperative AKI.

Keywords: Mannitol, acute kidney injury, AKI, AKI prevention, aortic surgery

What this paper adds:

Postoperative acute kidney injury is known as an independent risk factor for both short- and long-term mortality. The diuretic mannitol is often used in cardiovascular surgery and other surgical fields for renal protection. This systematic review substantiates that perioperative use of mannitol for AKI prevention should not be considered an evidence-based intervention in cardiac and vascular surgery, partial nephrectomy, and/or other major surgery. This seems because data mostly derive from heterogeneous cohorts with limited samples size. Further research seems required with a focus on high risk patients for postoperative AKI.

Introduction

Postoperative acute kidney injury (AKI) is a frequent complication and an independent risk factor for both short- and long-term morbidity and mortality. (1-4) The incidence of postoperative AKI is 20-37%(5) in open aortic repair, 20-30% in procedures performed with the use of cardiopulmonary bypass(6, 7) and 1% up to 32% in non-cardiac major surgery.(2-4) In 2-4% of vascular and cardiac surgery patients, renal replacement therapy (RRT) is needed(5). For cardiac surgery, AKI-related mortality of 4.5% is reported.(6) Although there is an urgent medical need for strategies to prevent perioperative AKI, most evaluated strategies have failed.(8-10) In some institutions, mannitol is used for perioperative renal protection in open aortic repair(11), in cardiopulmonary bypass procedures(12), in partial nephrectomy and in renal transplantation.(13)

Mannitol is a sugar alcohol used as an osmotic diuretic. The substance is freely filtered and does not undergo tubular reabsorption. It increases intratubular osmotic pressure, thus enhancing free water excretion.(14) Mannitol has been reported to induce renal vasodilatation by decreasing renal vascular resistance (RVR) and thereby increasing renal blood flow (RBF) (14, 15), however, results are inconclusive. (16) Data deriving from experiments in both humans and animals show that in general, mannitol does not affect glomerular filtration rates (GFR).(14-16) In hypoperfused kidneys, some evidence deriving from research in animals shows that mannitol may increase or restore GFR(14), an effect that may partly be explained by a reduction in tubular cell swelling(14, 17), and prostaglandin-mediated vasodilatation.(18) Intratubular hydrostatic pressures are elevated after mannitol infusion in hypoxic kidneys, which may theoretically prevent

swelling and obstruction of renal tubules.(14, 17) In a recent study, Damasceno-Ferreira et al. demonstrated in a pig model that mannitol could prevent glomerular loss during warm ischemia. (19) Clinical parameters including urea and creatinine concentrations did not change significantly. (19) Moreover, mannitol was proposed to act as an oxygen free radical scavenger attenuating ischaemia–reperfusion injury. (20-22) Haraldsson et. al. and Khoury et al. could observe an effect of mannitol on direct and indirect renal ischemia-reperfusion injury in animals (20, 22). Some thus speculate that mannitol may have “renal protective” effects. On the other hand, case reports and retrospective data report AKI and osmotic nephrosis related to mannitol in patients with stroke, intracerebral hemorrhage, or trauma, who received high dose mannitol to treat increased intracranial pressure. (23-26) Mannitol-induced renal injury was related to renal tubular vacuolization and swelling of tubular cells(25, 27), in a dose-dependent fashion. Other risk factors for mannitol associated renal injury are concomitant use of diuretics, diabetes, higher initial National Institutes of Health Stroke Scale (NIHSS) scores, and/or renal insufficiency at admission.(26) In most cases, mannitol-induced renal injury appears reversible after discontinuation. (25, 26)

Although evidence remains ambiguous, mannitol is frequently administered in the perioperative setting in an effort to prevent renal injury. We therefore conducted a systematic review to clarify whether there is evidence in favor of administering perioperative mannitol prophylactically for postoperative AKI.

Methods

This review was registered in the PROSPERO database (CRD42018099086), the international prospective register of systematic reviews. This article adheres to the applicable PRISMA guidelines on reporting items for Systematic Reviews and Meta-Analyses.(28)

Studies examining a potential influence of perioperative mannitol administration on postoperative renal function and published between January 1st, 1990 and October 2018, and were eligible for inclusion. Medline/Pubmed, Embase, the Cochrane Library, the Clinical Trials registry, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched using the terms “kidney”, “renal”, “perioperative” and “mannitol” either alone or in combination (JW, CAP). Further, we searched the reference lists of all initially identified reports to identify additional potential publications (JW, CAP).

Inclusion and exclusion criteria

According to the PRISMA checklist for transparent reporting of systematic reviews, publications were included in the final analysis if all of the following criteria were met: (1) population: studies involving adult patients undergoing surgery or a related intervention; (2) intervention: i.v. mannitol administered in either the pre-operative or intra-operative period with comparison to control subjects; (3) predefined outcomes: postoperative AKI or respective renal endpoints/surrogates. Studies with endpoints other than renal function (i.e.trials on mannitol in renal replacement therapy, on prevention of intracranial or intraocular pressure, or investigations on orally administered or inhaled mannitol) or

surrogates of renal function, and reports not written in English or German were excluded.

Data collection process

All potentially eligible papers were assessed in detail. Data extraction (JW) was performed using a predesigned form and checked by a second reviewer (CAP). The following data were extracted: first author, publication year, type of surgery or intervention, study intervention and control group, sample size, incomplete reporting, allocation and randomization, blinding, primary and secondary outcomes, follow-up period.

Bias

An attempt was made to minimize bias with a comprehensive search strategy including non-published data. Methodological quality and the risk of bias within the reviewed RCTs were assessed according to the Cochrane Handbook for Systematic Reviews of Interventions. (29) For this purpose, six items were evaluated for each study included: (I) random sequence generation and (II) allocation concealment (selection bias), (III) blinding of participants and personnel (performance bias), (IV) blinding of outcome assessment (detection bias), (V) incomplete outcome data (attrition bias) and (VI) selective reporting (reporting bias). The Assessment was performed independently by three authors (JW, ASM and CP).

Results

1,538 records were identified in the primary search after removal of duplicates (Fig. 1). After screening for eligibility, 1,505 publications were excluded based on the predefined inclusion and exclusion criteria. Thirty-three publications were evaluated in detail. After exclusion of another 11 records (full text not available in English or German, conference abstract with no full text published, mannitol applied postoperatively, no control group) (Fig. 1), 22 reports remained in the final analysis (17 prospective and/or randomized controlled trials [RCTs] and five retrospective studies).

Out of 22 reports in the final analysis, three RCTs and one retrospective study reported use of mannitol in elective open or endovascular repair of the abdominal aorta. The use of mannitol in elective cardiac surgery was studied in seven trials. The application of mannitol in extracorporeal shock wave lithotripsy (ESWL) was examined in two RCTs and in living donor kidney transplantation in one RCT. Two RCT and three retrospective studies evaluated the use of mannitol in partial nephrectomy. One RCT studied mannitol in liver transplantation and one in surgery for obstructive jaundice. One retrospective study evaluated mannitol in robot-assisted laparoscopic radical prostatectomy (RALP). The quality of RCTs included in our systematic review was assessed by the Cochrane Collaboration tool (29) (Table 3). Almost two thirds of the included RCTs are of unclear risk of bias (10/16). Six studies are of low risk for bias and one of high risk. Most often, uncertainty of bias was related to (I) random sequence generation, (II) allocation concealment (selection bias), (IV) blinding of outcome assessment (detection bias) and (V) incomplete outcome data (attrition bias) (Table 3, Figure 2). Most RCTs provided no power analysis and were of small size (median n=42, range 118-199). In total they

included 904 patients. Follow-up periods in the RCTs chosen were short (range 12h postoperatively until six months), whereas the sample size of the included retrospective studies(30-32) varied from n=55 to n=476 (median n=285), with a total of 1,569 patients. The follow-up period was up to 13 months. Further information is provided in Table 1 and 2.

Mannitol in vascular surgery

Three RCTs studied the effect of mannitol on AKI in vascular surgery.(33-35) Two of these were performed in patients with open aortic repair and infrarenal clamping and one in endovascular aortic repair (EVAR).

Nicholson et al. included 28 patients and compared 0.3g/kg mannitol as a rapid i.v. bolus before cross-clamping of the aorta against placebo.(35) Patients in the mannitol arm had lower levels of urinary albumin/creatinine ratio (160±32 vs. 500±140 mg/mmol; p=.04) and urinary N-acetyl-β-D-glucosaminidase (NAG)/creatinine ratio (143±34 vs. 271±70 pmol/mmol; p=.04) at 24 hours postoperatively. Differences in day 7 creatinine clearance and postoperative complications or mortality were not observed.(35)

Wijnen et al. compared a co-intervention with different anti-oxidative substances, including a mannitol infusion over 12 hours, with the authors' standard care. The authors reported an increased creatinine clearance on day 2 in patients receiving the intervention when compared to controls (106±90 vs. 73±76 ml/min/1,73m^2, p=.047), but this effect was not preserved through day 7.(34) In EVAR, 86 patients were treated with a mannitol bolus and hydration or with hydration alone.(33) When compared to controls, patients in the intervention arm had lower 24h serum creatinine (1.07±0.26 vs. 1.20±0.30mg/dl, p<.05). Serum-cystatin-C levels were lower in the mannitol group at 24

hours (2.2±0.8 vs. controls 2.6±0.9mg/l, p<.05) but not at 72 hours. No differences in AKI according to the RIFLE classification and no differences in urinary neutrophil gelatinase-associated lipocalin (NGAL) levels were observed.(33)

A retrospective study in 169 patients undergoing aortic repair with suprarenal clamping but without cold renal perfusion identified mannitol (0.5 g/kg, range 0.1-1.0 g/kg) as renoprotective (odds ratio [OR] 0.3; 95% confidence interval [CI] 0.1-0.8) for AKI development according to the RIFLE (Risk, Injury, Failure, Loss of kidney function, and endstage renal disease) classification.(30)

Mannitol in cardiac surgery

Several smaller studies were performed in cardiac surgery patients.

Fisher et al. compared different doses of mannitol vs. placebo. The group studied urinary output as a surrogate for renal function and showed an increase in urinary output in the mannitol group.(36)

A smaller study by Ip-Yam et al. compared mannitol 0.5 g/kg added to the cardiopulmonary bypass (CPB) prime in a normothermic group vs. a hypothermic regime and a standard-of-care regime. No differences were observed in creatinine clearance, fractional sodium excretion, microalbuminuria, or urinary NAG.(37)

Three other studies compared mannitol as an additive to the cardiopulmonary bypass (CBP) prime or as an infusion vs. mannitol plus dopamine infusion vs. dopamine alone or placebo.(38-40) Significant differences were not identified in any of the chosen surrogates of AKI, except for one study that found a significant increase in β2-microglobulin (β2M) in the dopamine groups (dopamine alone vs. placebo and

dopamine + mannitol vs. placebo: 2.48±3.61µg/min vs. 0.59±1.04 µg/min; p=.001 and 2.05±2.77µg/min vs 0.59±1.04 µg/min; p=.007) at one hour post-CBP.(40)

Yallop et al. and Smith et al. conducted high-quality studies in cardiac surgery patients with either normal creatinine baseline levels or established renal dysfunction (41, 42). Both studies revealed no differences in chosen surrogates of renal function within the first postoperative days.

Mannitol in renal surgery

Five RCTs and four retrospective studies investigated mannitol in urology. Muter et al. used the Doppler-based renal resistive index (RI) to evaluate potential renoprotective effects of mannitol in patients receiving ESWL.(43) A slightly lower RI was observed in patients receiving mannitol before ESWL when compared to controls.(43) Nevertheless, the clinical significance of this finding remains unclear.

Ogiste et al. used urinary β2-microglobulin(β2M)-to-creatinine ratio and the microalbumin-to-creatinine ratio as surrogates of kidney injury and found a significant increase in the urinary β2M-to-creatinine ratio directly after ESWL, but not on day 1 or 7.(44)

In renal transplantation, an RCT by Esfahani et al. evaluated mannitol versus no intervention in living donor kidney transplantation. No difference in the chosen endpoints (urine volume, serum urea and creatinine) under investigation were observed.(45)

A recent RCT by Spaliviero et al. studied potential effects of mannitol in nephron-sparing surgery (NSS) in 199 patients with preoperative estimated GFR (eGFR) >45 ml/min/1.73m^2. (46) The authors identified no significant differences in eGFR at 6 weeks or 6 months as well as in renal radionuclear scintigraphy scans at 6 months. In 65

patients who underwent robotic-assisted-laparoscopic partial nephrectomy (RALPN), Choi K et al. observed no difference between individuals receiving 12g mannitol vs. controls.(47)

Four retrospective studies showed no benefits of mannitol use in partial nephrectomy or RALPN. (31, 32, 48, 49)

In respective studies and the trial by Spaliviero et al., kidney hypothermia was at least partly used as an additional renoprotective measure, primarily in controls.(31, 32, 46)

Mannitol in liver surgery

Wahbah et al. evaluated different combinations of dopamine and mannitol vs. controls in obstructive jaundice.(50) No differences in any of the chosen endpoints were noted.(50) One study tested mannitol as a reno-protective agent in orthotopic liver transplantation, but the authors did not observe any between-group differences with regard to fluid balance, urinary output, or 24h creatinine clearance in a short-follow-up period .(51)

Discussion

Despite conflicting data (10), mannitol is still applied in clinical practice for prevention of postoperative AKI.(11-13) In the current systematic review, we analyzed data from 16 RCTs and 3 retrospective studies examining the effects of perioperative mannitol use in a broad spectrum of surgical fields. To date this is the largest review examining the effect of perioperative application of mannitol on AKI, with the broadest spectrum of surgical procedures.

In one retrospective study in open abdominal aortic surgery with suprarenal clamping, mannitol was identified as a potential renoprotective factor.(30) RCTs in vascular surgery and in ESWL observed effects related to early biomarkers of tubular cell damage.(33-35, 44) None of the RCTs observed any differences in AKI or patient-centered clinical outcome measures, such as postoperative complications or mortality. Two retrospective studies in partial nephrectomy revealed no benefits for mannitol either. This is supported by a meta-analysis by Yang et al. including only five perioperative trials and 215 patients,(52) which found no benefits for i.v. mannitol in terms of AKI prevention. No evidence was found in another review on mannitol in open abdominal aortic aneurysm surgery covering mostly older studies.(53)

When interpreting available data on the perioperative use of mannitol to prevent postoperative AKI, it is important to note that both potential (i.e., theoretical) benefits as well as mostly negative trial data for mannitol exist. There may be several reasons for this.

First, although AKI is a frequent postoperative complication with typical incidences ranging from 20-37% in high-risk surgery, most of the included RCTs appear to be

underpowered (Table 1), with only 904 patients from RCTs summarized in this review. Therefore, there is still a demand for larger, adequately powered studies to examine the pharmacological agents available for AKI prevention.(10)

Second, perioperative renal injury may result from multiple etiologies. Patient co-morbidities(54), pre-renal fluid status(8), inflammation(55), direct ischemia(30), ischemic embolism (56), influence of toxins or oxidative mechanisms (57) (58) and cardiac function (9) may all affect AKI development. Thus, mannitol could theoretically provide benefits for some but not all etiologies. Nevertheless, in combination with optimal goal-directed fluid therapy, mannitol may optimize RBF and renal function.(15) Yet without concomitant fluid therapy or in combination with other diuretics, mannitol may even worsen renal function, as seen for example in patients treated with mannitol for high intracranial pressure.(26)

Third, careful patient selection may be key for a strategy to prevent AKI. In procedures with a higher risk of postoperative renal injury, such as aortic surgery and suprarenal clamping, mannitol may be protective. Furthermore, alternative methods for renal protection, such as cold kidney perfusion, may abolish potential protective effects of mannitol, even with similar or prolonged clamping times. This may at least partially explain the contradictory results of the retrospective studies.(30-32)

Fourth, measurement of glomerular filtration rates could be regarded as gold standard for assessment of renal function. Given that this is unpractical for perioperative use, most investigations used serum creatinine or urine output to assess renal function. Thus, the authors adhere to the Kidney Disease Improving Global Outcome (KDIGO) Clinical Practice Guidelines that define changes in serum creatinine levels and/or (de-creased)

urinary volumes as the most relevant indices in AKI .(59) Nevertheless, changes in creatinine and/or decrease in urinary output are regarded as late (functional) markers of renal dysfunction. (60) and diagnosis of AKI based on creatinine (or urine output) may thus underestimate renal damage, especially in short observational periods in non-steady state conditions.(10, 60)

In an effort to detect AKI early, several new biomarkers were proposed in the last years.(61) Some were tested in studies included in this review (e.g. NGAL, Cystatin C and others). (33, 35, 37-39) Among these, Cystatin C and NGAL might be most promising. Cystatin C, a 13-kDa protein is freely filtered, reabsorbed, and metabolized in the proximal tubule.(62, 63) Serum, Cystatin C levels correlate well with GFR and increased urinary Cystatin C excretion reflects AKI as its uptake is reduce by damaged tubules. (62, 63) With a Cystatin C half-life of about one third of the half-life of creatinine, steady state conditions may be reached faster.(64) NGAL is a 25-kDa protein from human neutrophils. (62) Increased NGAL concentrations in urine and plasma were shown to reflect AKI and predict adverse clinical outcomes (e.g. need for RRT, mortality). (62, 63)

Nevertheless, although new biomarkers appear promising, it appears that further research is required before they could be applied in daily clinical use. The matrix of testing, AKI-related specificity, and potential confounding medications could influence cutoffs and diagnostic value. (62-64)

Limitations to this analysis include the fact that we deliberately restricted our literature research to studies performed after 1990 assuming that surgical technique, anesthesiological management and study design has evolved in the last 30 years.

Furthermore, studies included appear heterogeneous with regard to different mannitol regimes applied, different endpoints, and different sample sizes. Due to this heterogeneity, performing of a meta-analysis did not seem reasonable.

Moreover, we found a retrospective study (Reese J. et al., *The Journal of Urology*. 2017;197(4S): e1273) of mannitol in partial nephrectomy which was published as abstracts only and was therefore not included . Nevertheless, the respective study showed no benefit of mannitol.

Conclusions

Despite theoretical benefits, current evidence does not support the use of mannitol as a renal protective perioperative measure in cardiopulmonary bypass procedures, partial nephrectomy, or other major types of surgery. Some evidence hints at a potential benefit in abdominal aortic surgery, especially in patients with suprarenal clamping. Further adequately powered studies are required to determine whether there is a place for mannitol in the perioperative setting in specific indications.

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	Surgery	Intervention	Control	Sample size	Blinding, Random-ization	Outcome, Follow-Up
Nicholson et al. 1996 (28)	Elective aortic repair, infra-renal clamp	Mannitol 0.3g/kg i.v. before cross-clamping	Normal saline	n=28, (1:1)	Unblinded. Randomized (sealed envelope).	Urine output, CrCl, BUN, sCr, urinary albumin and uNAG. LOS in ICU. Until 7th day
Wijnen et al. 2001 (42)	Elective open infra-renal aortic repair	Antioxidants: vitamine E, vitamine C, allo-purinol, N-acetylcysteine, mannitol 0.5g/ 12h	Standard-of care-therapy	n=42 (1:1)	Unblinded. Randomized (method not mentioned).	CrCl, microalbumin in urine. Until 7th day post-surgery
Kalimeris et al. 2014 (27)	Endo-vascular aortic repair (EVAR)	Mannitol 0.5g/kg i.v. + hydration (500ml Ringer's lactate + 2ml/kg/h + losses)	Hydration	n=86 (1:1)	Unblinded. Randomized (sealed envelope).	Primary Outcome: sCR, AKI (RIFLE criteria), secondary outcomes: Serum-Cystatin-C, urinary NGAL at 24 + 72h
Narin et al. 2015 (36)	Elective CABG-surgery	Group I : mannitol 1g/kg in CPB-prime. II:DA 2 µg/kg/min i.v. III: DA + mannitol.	IV: furo-semide i.v. (low urinary output)	n=100, (1:1)	Unblinded. Unclear or no randomi-zation.	Urinary microalbumin, urinary creatinine and serum cystatin-c values. Until 2nd day
Yallop et al. 2008 (29)	Elective cardiac surgery in patients with normal baseline creatinine	5 ml/kg mannitol in CPB-prime	Ringer's lactate added to CBP-prime	n=40 (1:1)	Blinded (except perfusionist). Randomized (Computer-generated random number)	Retinol binding protein (RBP), microalbumin; sCr; blood urea nitrogen (BUN); urine-output, fluid balance. Until 5th day
Smith et al. 2008 (30)	Elective CABG in patients with established renal dysfunction	0.5g/kg mannitol (CPB-prime)	Ringer's lactate (CBP-prime)	n= 47 (1:1)	Blinded (except perfusionist). Randomized (random number)	Daily urine output, fluid intake, plasma creatinine, urea. Until 3rd day.
Carcoana et al. 2003 (35)	Elective, primary CABG requiring CPB.	Group 2: mannitol 1 g/kg (CBP-prime) + placebo-infusion, group 3: DA 2µg/kg/min + placebo (CBP-prime) group 4: DA + mannitol	Group 1): normal saline as infusion and added to CBP-prime	n=100 (1:1:1:1)	Double-blinded. Randomized (random-number tables)	Primary outcome: β2M 1h post-CBP; secondary outcome: β2M at 6 + 24h, CrCl, sCr, urinary flow rates, LenghOS-ICU, hospitalization, clinical events. Until hospital discharge
Dural et al. 1999(31)	Elective coronary artery surgery	Group I : DA 3µg/kg/min i.v. Group II: mannitol 1 mg/kg/h i.v.	Group III: standard-of-care	n=36 , (1:1:1)	Unblinded. Randomized (method not mentioned).	NAG activity, levels of serum, urinary creatinine, and BUN. Until 2nd day
Fisher et al. 1998(43)	Elective CABG surgery	Group 2: 10 g mannitol (CBP-prime) 3: 20g mannitol added 4: 30g mannitol added	Group 1: no mannitol added	n=76 (1:1:1:1)	Unblinded. Randomized (method not mentioned).	Urine output. 12h after surgery

	Surgery	Intervention	Control	Sample size	Blinding, Random-ization	Outcome, Follow-Up
Ip-Yam et al. 1994(44)	Elective CABG surgery	Group H: moderate hypothermia (28°C) Group M: 37°C + mannitol 0.5g/kg (CPB prime)	Group N: 37°C + no mannitol	n=24 (1:1:1)	Unblinded. Randomized (method not mentioned).	sCr, sNa, urinary NAG and microalbumin, CrCl, FEN. Until 6th day
Esfahani et al. 2014 (32)	Living Donor Kidney Trans-plantation	Mannitol, dose not mentioned	No Mannitol	n=60, (1:1)	Blinded data-collection. Randomized (alternating numbers).	Urine-volume (first 24h), BUN, sCr. Until hospital discharge
Muter et al. 2009(37)	ESWL	0.5g/kg mannitol immediately before ESWL	Non	n=38 (1:1)	Unblinded. Randomized (method not mentioned).	Renal resistive index. Until day 7
Ogiste et al. 2003(45)	ESWL	0.5 g/kg mannitol i.v. immediately before ESWL	Non	n=18, (1:1)	Unblinded. Randomized (method not mentioned).	β2M and microalbumin. 7th day after procedure
Spaliviero et al. 2017 (33)	Nephron sparing surgery in renal mass	Mannitol 12.5g i.v. within 30 min prior renal vascular clamping	Normal saline	n=199 (1:1)	Double-blinded. Randomized (permuted blocks)	sCR and eGFR, split function on 6-mo renal scan, grade 3–5 complications within 30 d of surgery.
Choi et al 2018	RALPN	12 g mannitol in 50 ml normal saline	50 ml normal saline	n=79 n=65 analysed (1.1:1)	Double-blinded. Computer-generated randomized schedule	Primary outcome: GFR at 24 h,1 week, and 30 days Secondary outcome: percent change in eGFR at 24 h, 1 week, and 30 days, complications and readmissions
Whitta et al. 2001(34)	Orthotopic liver trans-plantation	0.5 g/kg mannitol i.v.	Normal saline	n=25 (1:1)	Double-blinding. Randomized (random number)	24hours-creatinine-clearance, fluid intakes, urine output. 24h postoperative.
Wahbah et al. 2000(38)	Surgery in obstructive jaundice	Group II: DA 2.5µg/kg/min i.v. III: DA + mannitol 0.25mg/kg i.v. IV: DA +furosemide 1mg/kg i.v.	Group I: controls, fluid therapy only	n=40, (1:1:1:1)	Unblinded. Randomized (method not mentioned).	24h-urine-output, sCr, creatinine-clearance. Until day 7.

Table 1

	Surgery	Intervention	Control	Sample size	Blinding, Random-ization	Outcome, Follow-Up
Dubois et al. 2013(39)	Elective juxta-renal aortic repair Retro-spective study	Mannitol 0.5 g/kg (range, 0.1-1.0 g/kg) i.v.	No mannitol.	n=169 (3:1)	n.a.	Postoperative renal dysfunction classified (RIFLE criteria). Until hospital discharge
Omae et al. 2014(40)	Open partial nephrectomy. Retrospective study.	Mannitol 20% 100ml 15min before X-Clamping	No mannitol.	n=55: (1:1.5)	n.a.	eGFR. Until 6th month.
Power et al. 2012(41)	Minimal invasive partial nephrectomy. Retrospective study.	12.5g mannitol i.v.	No mannitol.	n=285, (1.4:1)	n.a.	eGFR. Up to 13 months.
Cooper et al 2018	Partial nephrectomy Retrospective study.	Mannitol (12.5 and 25g)	No Mannitol	n=476 (1.5:1)	n.a.	eGFR at 6 months
Kong et al. 2018	RALP Retrospective study.	Mannitol 0.5 g/kg	No Mannitol	n=468 (1:1)	n.a.	AKI according KDIGO, LOS Hospital, ICU admission rate, LOS ICU Up to 12 months

Table 2

Study	Selection bias: Random sequence generation	Selection bias: Allocation concealment	Performance bias: Blinding of participants and personnel	Detection bias: Blinding of outcome assessment	Attrition bias: Incomplete outcome data	Reporting bias: Selective reporting	*Summary assessment Risk of bias*
Kalimeris et al. 2014	+	+	−	−	+	+	?
Wijnen et al. 2002	?	?	−	?	?	+	?
Nicholson et al. 1996	+	+	?	?	?	+	?
Yallop et al 2008	+	+	+	?	?	+	+
Smith et al 2008	+	+	+	?	?	+	+
Carcoana et al 2003	+	+	+	?	+	+	+
Dural et al. 1999	+	+	?	?	?	+	+
Fisher et al. 1998	?	?	?	?	?	+	?
Ip-Yam et al. 1994	?	?	−	?	?	+	?
Esfahani et al. 2014	−	−	−	+	?	+	−
Muter et al. 2009	?	?	−	?	+	+	?
Ogiste et al. 2003	?	?	−	?	+	+	?
Whitta et al. 2001	?	?	+	?	?	+	?
Wahbah et al. 2000	?	?	?	?	?	+	?
Spaliviero et al. 2018	+	+	+	+	+	+	+
Choi et al. 2018	+	+	+	?	−	+	+

Table 3

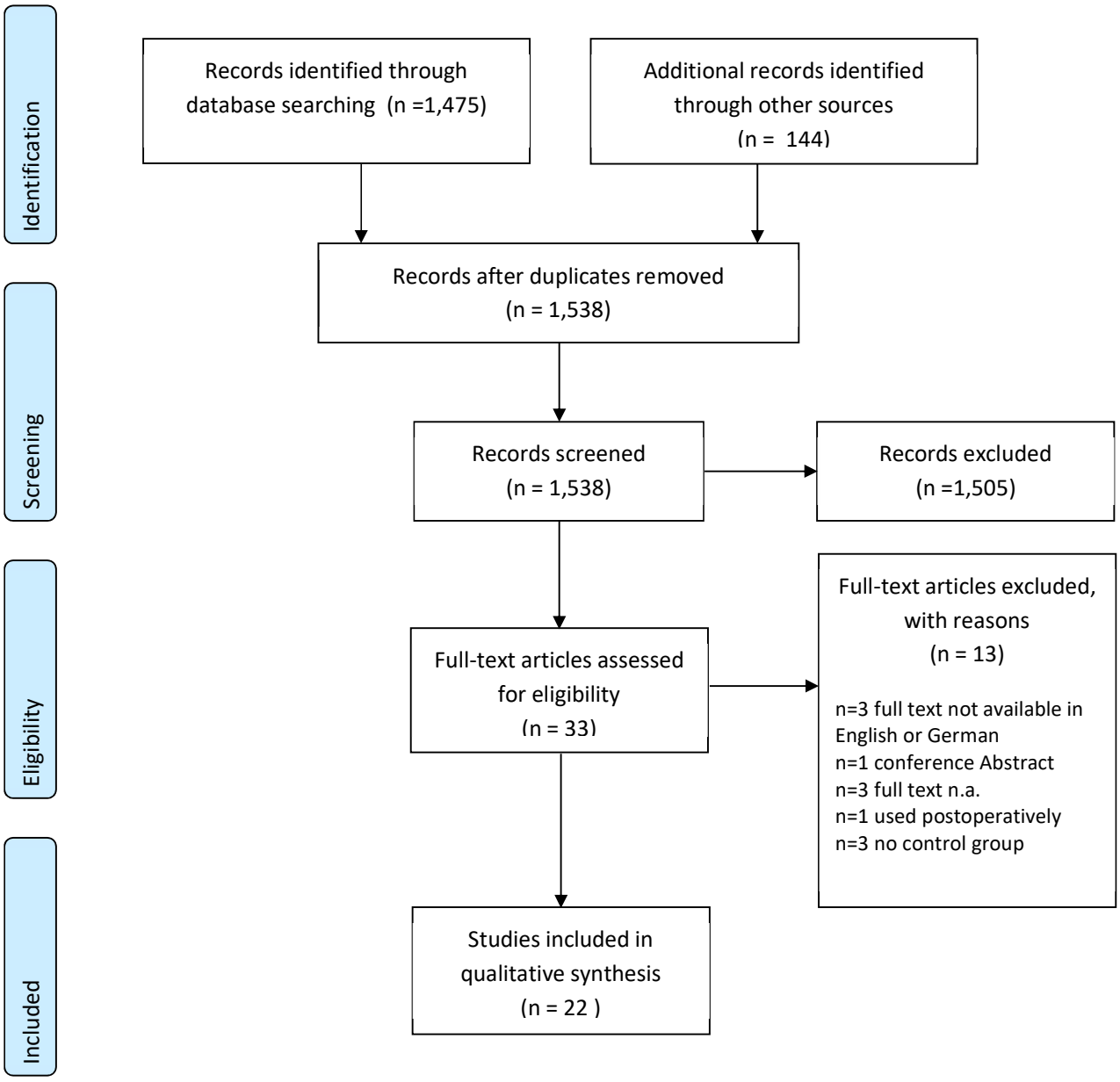
Identification
Screening
Eligibility
Included
Records identified through database searching (n =1,475)
Additional records identified through other sources (n = 144)
Records after duplicates removed (n = 1,538)
Records screened (n = 1,538)
Records excluded (n =1,505)
Full-text articles assessed for eligibility (n = 33)
Full-text articles excluded, with reasons (n = 13)
n=3 full text not available in English or German
n=1 conference Abstract
n=3 full text n.a.
n=1 used postoperatively
n=3 no control group
Studies included in qualitative synthesis (n = 22)

Figure 1

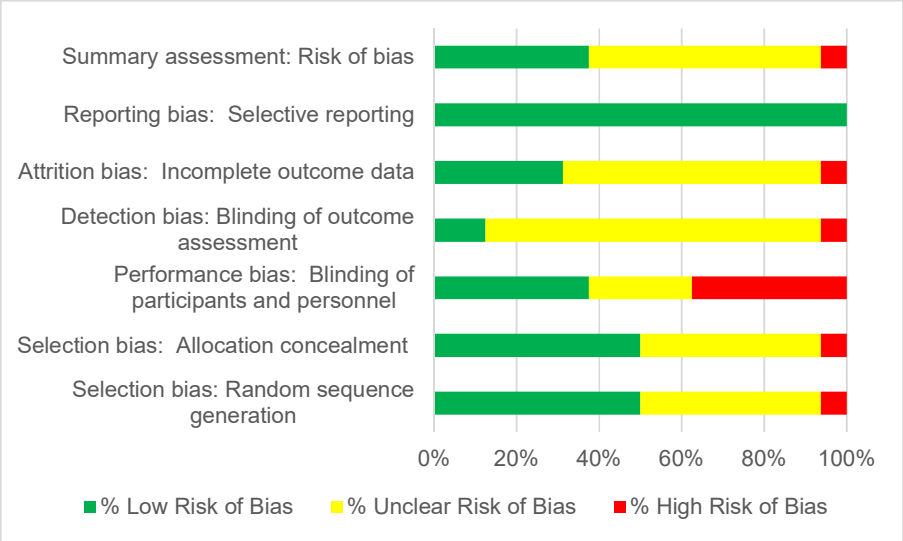

Figure 2

Figure and table legends

Figure 1: PRISMA flowchart

Figure 2: Risk of bias about each risk of bias item and overall risk of bias presented as percentages across all included RCTs.

Table 1: Characteristics of prospective trials included

β2M = β2-microglobulin, BUN = blood urea nitrogen, CABG = coronary artery bypass graft, CPB = cardiopulmonary bypass, DA = dopamine, ESWL = extracorporeal shock wave lithotripsy, LOS = length of stay, uNAG = urinary N-acetylglucosaminidase, uNGAL = urinary neutrophil gelatinase-associated lipocalin, RALPN = robotic assisted laparoscopic partial nephrectomy, RIFLE = Risk/Injury/Failure/Loss/Endstage, sCR = serum creatinine, n.a. = not applicable, FEN = fractional excretion of sodium.

Table 2: Characteristics of retrospective studies included

AKI = acute kidney injury, eGFR = estimated glomerular filtration rate, ICU = Intensive Care Unit, KDIGO = Kidney Disease Improving Global Outcomes; LOS = length of stay, RALP = robotic assisted laparoscopic prostatectomy, RIFLE = Risk/Injury/Failure/Loss/Endstage

Table 3: Assessment of risk of bias for each RCT:  = low risk of bias;  = unclear risk of bias.;  = high risk of bias