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SYSTEMATIC REVIEW

Mannitol for the Prevention of Peri-Operative Acute Kidney Injury: A Systematic Review

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WHAT THIS PAPER ADDS

Post-operative acute kidney injury (AKI) is known to be 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 peri-operative 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 is because data mostly derive from heterogeneous cohorts with limited samples size. Further research is required with a focus on patients at high risk of post-operative AKI.

Objective/Background: Post-operative acute kidney injury (AKI) is a frequent peri-operative complication that negatively affects morbidity and mortality. Mannitol is frequently used peri-operatively for renal protection, although evidence for its use is ambiguous. A systematic review was conducted to clarify whether there is evidence supporting peri-operative mannitol administration for the prevention of post-operative AKI.

Methods: 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 (i) population (studies involving adult patients undergoing surgery or a related intervention); (ii) intervention (intravenous mannitol administered in either the pre- or intra-operative period with comparison to controls); and (iii) predefined outcomes (post-operative AKI or respective renal end points/surrogates).

Results: In total, 1,538 articles published between January 1990 and October 2018 were identified. After checking for eligibility, 22 studies, including 17 prospective and/or randomised controlled trials and five 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.

Conclusion: Given the available evidence, the peri-operative 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 of post-operative AKI.

Keywords: Acute kidney injury, Aortic surgery, AKI, AKI prevention, Mannitol
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INTRODUCTION

Post-operative 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 post-operative AKI is 20—37% in open aortic repair,[5] 20—30% in procedures performed with the use of cardiopulmonary bypass,[6,7] and 1—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 peri-operative AKI, most evaluated strategies have failed.[8—10] In some institutions, mannitol is used for peri-operative renal protection in open aortic repair,[11] in cardiopulmonary bypass

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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 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 be explained partly 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 ischaemia.[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 ischaemia reperfusion injury in animals.[20,22] Thus, some speculate that mannitol may have "renal protective" effects. However, case reports and retrospective data report AKI and osmotic nephrosis related to mannitol in patients with stroke, intracerebral haemorrhage, or trauma, who received high dose mannitol to treat increased intracranial pressure.[23–26] Mannitol induced renal injury was related to renal tubular vacuolisation 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 scores, and/or renal insufficiency on 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 peri-operative setting in an effort to prevent renal injury. Therefore, a systematic review was conducted to clarify whether there is evidence in favour of administering peri-operative mannitol prophylactically for post-operative 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 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines on reporting items for systematic reviews and meta-analyses.[28]

Studies examining a potential influence of peri-operative mannitol administration on post-operative renal function and published between 1 January 1990 and October 2018 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", "peri-operative", and "mannitol", either alone or in combination, by two authors (J.W., C.A.P.). Further, the reference lists of all initially identified reports were searched (by J.W. and C.A.P.) to identify additional potential publications.

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: (i) population: studies involving adult patients undergoing surgery or a related intervention; (ii) intervention: intravenous mannitol administered in either the pre- or intra-operative period with comparison to controls; (iii) predefined outcomes: post-operative AKI or respective renal end points/surrogates. Studies with end points 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 was performed by one of the authors (J.W.) using a predesigned form and checked by a second reviewer (C.A.P.). 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 randomisation, blinding, primary and secondary outcomes, and follow up period.

Bias

An attempt was made to minimise bias with a comprehensive search strategy including non-published data. Methodological quality and the risk of bias within the reviewed randomised controlled trials (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 (J.W., A.S.M., C.A.P.).

RESULTS

In total, 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

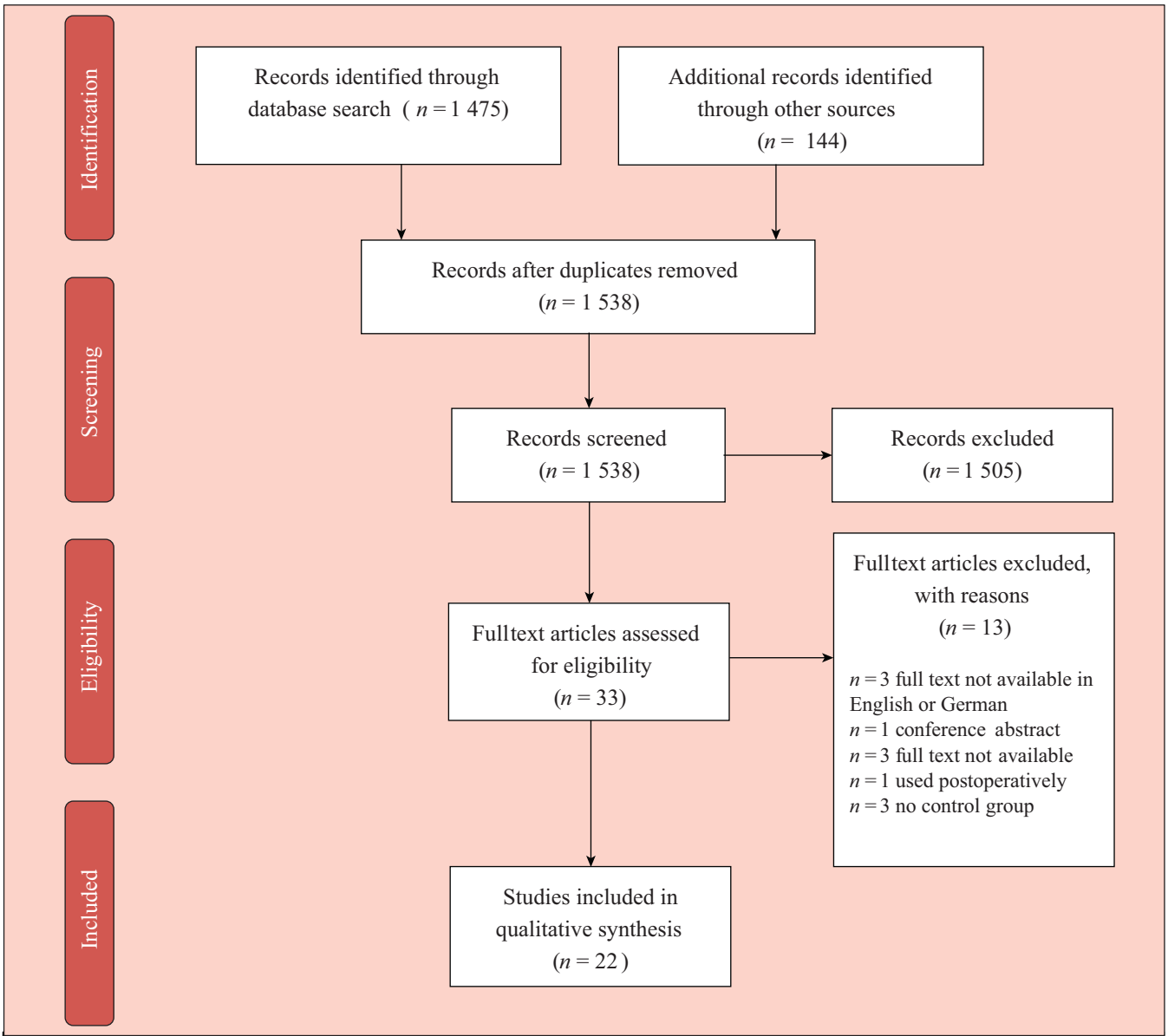

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart to identify studies on peri-operative mannitol administration for the prevention of post-operative acute kidney injury.

predefined inclusion and exclusion criteria. Thirty-three publications were evaluated in detail. After the exclusion of another 11 records (full text not available in English or German, conference abstract with no full text published, mannitol applied post-operatively, no control group [Fig. 1]), 22 reports remained in the final analysis (17 prospective and/or RCTs, and five retrospective studies).

Of the 22 reports included 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 RCTs 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 the systematic review was assessed by the Cochrane Collaboration tool (Table 1).[29] Almost two thirds of the included RCTs were of unclear risk of bias (n = 10/16), six studies were of low risk of bias and one was of high risk. Most often, uncertainty of bias was related to (i) random sequence generation; (ii) allocation concealment (selection bias); (iii) blinding of outcome assessment (detection bias); and (iv) incomplete outcome data (attrition bias; Table 1, Fig. 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 12 h post-operatively to six months), whereas the

Table 1. Risk of bias assessment for each included randomised controlled trial on peri-operative mannitol administration for the prevention of post-operative acute kidney injury

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[33]	+	+	−	−	+	+	?
Wijnen *et al.*, 2002[34]	?	?	−	?	?	+	?
Nicholson *et al.*, 1996[35]	+	+	?	?	?	+	?
Yallop *et al.*, 2008[41]	+	+	+	?	?	+	+
Smith *et al.*, 2008[42]	+	+	+	?	?	+	+
Carcoana *et al.*, 2003[40]	+	+	+	?	+	+	+
Dural *et al.*, 2000[39]	+	+	?	?	?	+	+
Fisher *et al.*, 1998[36]	?	?	?	?	?	+	?
Ip-Yam *et al.*, 1994[37]	?	?	−	?	?	+	?
Esfahani *et al.*, 2014[45]	−	−	−	+	?	+	−
Muter *et al.*, 2009[43]	?	?	−	?	+	+	?
Ogiste *et al.*, 2003[44]	?	?	−	?	+	+	?
Whitta *et al.*, 2001[51]	?	?	+	?	?	+	?
Wahbah *et al.*, 2000[50]	?	?	?	?	?	+	?
Spaliviero *et al.*, 2018[46]	+	+	+	+	+	+	+
Choi *et al.*, 2018[47]	+	+	+	?	−	+	+

+ = low risk of bias; ? = unclear risk of bias; − = high risk of bias.

sample size of the included retrospective studies varied from 55 to 476 (median 285),[30–32] with a total of 1,569 patients. The follow up period was up to 13 months. Further information is provided in Tables 2 and 3.

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 0.3 g/kg mannitol as a rapid intravenous 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 post-operatively. Differences in day 7 creatinine clearance and post-operative 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.[34] The authors reported an increased creatinine clearance on day two in patients receiving the intervention vs. controls (106 ± 90 vs. 73 ± 76 mL/min/L, 73 m^2; $p = .047$), but this effect was not preserved through to day seven.[34] In EVAR, 86 patients were treated with a mannitol bolus and hydration or with hydration alone.[33] When compared with controls, patients in the intervention arm had lower 24 hour serum creatinine (1.07 ± 0.26 vs. 1.20 ± 0.30 mg/dL; $p < .05$). Serum cystatin C levels were lower in the mannitol group at 24 hours (2.2 ± 0.8 vs. controls 2.6 ± 0.9 mg/L; $p < .05$) but not at 72 hours. No differences in

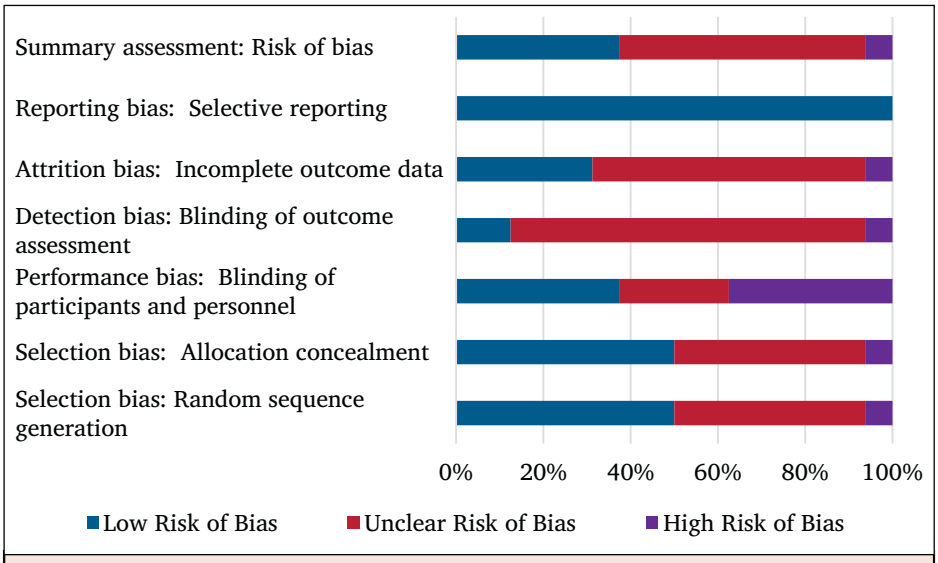

Figure 2. Risk of bias for each risk of bias item and overall risk of bias presented as percentages across all included randomised controlled trials on peri-operative mannitol administration for the prevention of post-operative acute kidney injury.

AKI according to the RIFLE (Risk, Injury, Failure, Loss of kidney function, and End stage renal disease) 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 classification.[30]

Mannitol in cardiac surgery

Several smaller studies were performed in cardiac surgery patients.

Fisher *et al.* compared different doses of mannitol with 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 regimen and a standard of care regimen.[37] No differences were observed in creatinine clearance, fractional sodium excretion, microalbuminuria, or urinary NAG.

Three other studies compared mannitol as an additive to the cardiopulmonary bypass (CPB) 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 $\pm$ 3.61 μg/min vs. 0.59 $\pm$ 1.04 μg/min [$p = .001$] and 2.05 $\pm$ 2.77 μg/min vs. 0.59 $\pm$ 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 post-operative 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 the potential renoprotective effects of mannitol in patients receiving ESWL.[43] A slightly lower RI was observed in patients receiving mannitol before ESWL when compared with controls. Nevertheless, the clinical significance of this finding remains unclear.

Ogiste *et al.* used urinary 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 one or seven.[44]

In renal transplantation, a RCT by Esfahani *et al.* evaluated mannitol vs. no intervention in living donor kidney transplantation. No difference in the chosen end points (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 in 199 patients with a pre-operative estimated GFR (eGFR) $>$ 45 mL/min/1.73 m^2.[46] The authors identified no significant differences in eGFR at six weeks or six months, or on renal radionuclear scintigraphy scans at six months. In 65 patients who underwent robotic assisted laparoscopic partial nephrectomy (RALPN), Choi *et al.* observed no difference between individuals receiving 12 g mannitol vs. controls.[47]

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

Table 2. Characteristics of included trials on peri-operative mannitol administration for the prevention of post-operative acute kidney injury

Study	Surgery	Intervention	Control	Sample size (randomization ratio)	Blinding, randomisation	Outcome, follow up
Nicholson *et al.*, 1996[35]	Elective aortic repair, infrarenal clamp	Mannitol 0.3 g/kg intravenously (i.v.) before cross clamping	Normal saline	$n = 28$ (1:1)	Unblinded; randomised (sealed envelope)	Urine output, creatinine clearance (CrCl), blood urea nitrogen (BUN), serum creatinine (sCr), urinary albumin, urinary *N*-acetylglucosaminidase; Length of stay (LOS) in intensive care unit (ICU) until day 7
Wijnen *et al.*, 2002[34]	Elective open infrarenal aortic repair	Antioxidants: vitamin E, vitamin C, allo-purinol, *N*-acetylcysteine, mannitol 0.5 g/12 h	Standard of care therapy	$n = 42$ (1:1)	Unblinded; randomised (method not mentioned)	CrCl, microalbumin in urine; Until day 7 post-surgery
Kalimeris *et al.*, 2014[33]	Endovascular aortic repair	Mannitol 0.5 g/kg i.v. + hydration (500 mL Ringer's lactate + 2 mL/kg/h + losses)	Hydration	$n = 86$ (1:1)	Unblinded; randomised (sealed envelope)	Primary outcome: sCR, acute kidney injury (Risk/Injury/Failure/Loss/End stage criteria), secondary outcomes: serum cystatin C, urinary neutrophil gelatinase associated lipocalin at 24 + 72 h
Narin *et al.*, 2015[38]	Elective coronary artery bypass graft (CABG) surgery	Group 1: mannitol 1 g/kg in cardiopulmonary bypass (CPB) prime; group 2: dopamine (DA) 2 μg/kg/min i.v.; group 3: DA + mannitol	Group 4: furosemide i.v. (low urinary output)	$n = 100$ (1:1:1:1)	Unblinded; unclear or no randomisation	Urinary microalbumin, urinary creatinine, and serum cystatin C values; Until day 2
Yallop *et al.*, 2008[41]	Elective cardiac surgery in patients with normal baseline creatinine	5 mL/kg mannitol in CPB prime	Ringer's lactate added to CPB prime	$n = 40$ (1:1)	Blinded (except perfusionist); randomised (computer generated random number)	Retinol binding protein, microalbumin; sCr; BUN; urine output, fluid balance; Until day 5
Smith *et al.*, 2008[42]	Elective CABG in patients with established renal dysfunction	0.5 g/kg mannitol (CPB prime)	Ringer's lactate (CPB prime)	$n = 47$ (1:1)	Blinded (except perfusionist); randomised (random number)	Daily urine output, fluid intake, plasma creatinine, urea; Until day 3
Carcoana *et al.*, 2003[40]	Elective, primary CABG requiring CPB	Group 2: mannitol 1 g/kg (CPB-prime) + placebo-infusion; group 3: DA 2 μg/kg/min + placebo (CPB prime); group 4: DA + mannitol	Group 1: normal saline as infusion and added to CPB prime	$n = 100$ (1:1:1:1)	Double blinded; randomised (random-number tables)	Primary outcome: β2-microglobulin (β2M) 1 h post-CPB; secondary outcome: β2M at 6 + 24 h, CrCl, sCr, urinary flow rates, LOS in ICU, hospitalisation, clinical events; Until hospital discharge
Dural *et al.*, 2000[39]	Elective coronary artery surgery	Group 1: DA3 μg/kg/min i.v.; group 2: mannitol 1 mg/kg/h i.v.	Group 3: standard of care	$n = 36$, (1:1:1)	Unblinded; randomised (method not mentioned)	*N*-acetylglucosaminidase activity, levels of serum, urinary creatinine, and BUN; Until day 2

Continued

Table 2-*continued*

Study	Surgery	Intervention	Control	Sample size (randomization ratio)	Blinding, randomisation	Outcome, follow up
Fisher *et al.* 1998[36]	Elective CABG surgery	Group 2:10 g mannitol (CPB prime); Group 3: 20 g mannitol added; group 4: 30 g mannitol added	Group 1: no mannitol added	$n = 76$ (1:1:1:1)	Unblinded; randomised (method not mentioned)	Urine output; 12 h after surgery
Ip-Yam *et al.*, 1994[37]	Elective CABG surgery	Group H: moderate hypothermia (28 °C); group M: 37 °C + mannitol 0.5 g/kg (CPB prime)	Group N: 37 °C + no mannitol	$n = 24$ (1:1:1)	Unblinded; randomised (method not mentioned)	sCr, serum sodium, urinary *N*-acetylglucosaminidase and microalbumin, CrCl, fractional excretion of sodium; Until day 6
Esfahani *et al.*, 2014[45]	Living donor kidney transplantation	Mannitol dose not mentioned	No Mannitol	$n = 60$, (1:1)	Blinded data collection; randomised (alternating numbers)	Urine volume (first 24 h), BUN, sCr; Until hospital discharge
Muter *et al.*, 2009[43]	Extracorporeal shock wave lithotripsy (ESWL)	0.5 g/kg mannitol immediately before ESWL	Undefined	$n = 38$ (1:1)	Unblinded; randomised (method not mentioned)	Renal resistive index; Until day 7
Ogiste *et al.*, 2003[44]	ESWL	0.5 g/kg mannitol i.v. immediately before ESWL	Undefined	$n = 18$ (1:1)	Unblinded; randomised (method not mentioned)	β2M and microalbumin; Day 7 after procedure
Spaliviero *et al.*, 2018[46]	Nephron sparing surgery in renal mass	Mannitol 12.5 g i.v. within 30 min prior renal vascular clamping	Normal saline	$n = 199$ (1:1)	Double blinded; randomised (permuted blocks)	sCR and estimated glomerular filtration rate (GFR), split function on 6 month renal scan, grade 3–5 complications within 30 d of surgery
Choi *et al.*, 2018[47]	Robotic assisted laparoscopic partial nephrectomy	12 g mannitol in 50 mL normal saline	50 mL normal saline	$n = 79$ $n = 65$ analysed (1.1:1)	Double blinded; computer generated randomised schedule	Primary outcome: GFR at 24 h,1 week, and 30 days. Secondary outcome: percentage change in estimated GFR at 24 h, 1 wk, and 30 d, complications, and readmissions
Whitta *et al.*, 2001[51]	Orthotopic liver trans-plantation	0.5 g/kg mannitol i.v.	Normal saline	$n = 25$ (1:1)	Double blinded; randomised (random number)	24 h creatinine clearance, fluid intakes, urine output; 24 h post-operatively
Wahbah *et al.*, 2000[50]	Surgery in obstructive jaundice	Group 2: DA 2.5 µg/kg/min i.v.; group 3: DA + mannitol 0.25 mg/kg i.v.; group 4: DA + furosemide 1 mg/kg i.v.	Group 1: controls, fluid therapy only	$n = 40$, (1:1:1:1)	Unblinded; randomised (method not mentioned)	24 h urine output, sCr, creatinine clearance; Until day 7

i.v. = intravenous; CrCl = creatinine clearance; BUN = blood urea nitrogen; sCr = serum creatinine; LOS = length of stay; ICU = intensive care unit; DA = dopamine; CPB = cardiopulmonary bypass; CABG = coronary artery bypass graft; β2M = β2-microglobulin; ESWL = extracorporeal shock wave lithotripsy; GFR = glomerular filtration rate.

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 end points were noted.

Table 3. Characteristics of included retrospective studies on peri-operative mannitol administration for the prevention of post-operative acute kidney injury

Study	Surgery	Intervention	Control	Sample size (randomization ratio)	Blinding, randomisation	Outcome, follow up
Dubois *et al.*, 2013[30]	Elective juxtarenal aortic repair Retrospective study	Mannitol 0.5 g/kg (range 0.1–1.0 g/kg) intravenously (i.v.)	No mannitol	$n = 169$ (3:1)	Not applicable (NA)	Post-operative renal dysfunction classified (Risk/Injury/Failure/Loss/End stage criteria); Until hospital discharge
Omae *et al.*, 2014[31]	Open partial nephrectomy Retrospective study	Mannitol 20% 100 mL 15 min before cross clamping	No mannitol	$n = 55$ (1:1.5)	NA	Estimated glomerular filtration rate (eGFR); Until month 6
Power *et al.*, 2012[32]	Minimally invasive partial nephrectomy Retrospective study	12.5 g mannitol i.v.	No mannitol	$n = 285$ (1.4:1)	NA	eGFR; Up to 13 months
Cooper *et al.*, 2018[48]	Partial nephrectomy Retrospective study	Mannitol (12.5 and 25 g)	No mannitol	$n = 476$ (1.5:1)	NA	eGFR at six months
Kong *et al.*, 2018[49]	Robotic assisted laparoscopic prostatectomy Retrospective study	Mannitol 0.5 g/kg	No mannitol	$n = 468$ (1:1)	NA	Acute kidney injury according to Kidney Disease Improving Global Outcomes, length of stay (LOS) in hospital, intensive care unit (ICU) admission rate, LOS in ICU; Up to 12 months

NA = not applicable; eGFR = estimated glomerular filtration rate; LOS = length of stay; ICU = intensive care unit.

One study tested mannitol as a renoprotective agent in orthotopic liver transplantation, but the authors did not observe any between group differences with regard to fluid balance, urinary output, or 24 hour creatinine clearance in a short follow up period.[51]

DISCUSSION

Despite conflicting data,[10] mannitol is still used in clinical practice for prevention of post-operative AKI.[11–13] In the current systematic review, data from 16 RCTs and three retrospective studies examining the effects of peri-operative mannitol use in a broad spectrum of surgical fields were analysed. To date this is the largest review examining the effect of peri-operative 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 centred clinical outcome measures, such as post-operative 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 peri-operative trials and 215 patients,[52] which found no benefits for intravenous 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 peri-operative use of mannitol to prevent post-operative AKI, it is important to note that there exist both potential (i.e. theoretical) benefits, as well as mostly negative trial data for mannitol. There may be several reasons for this.

Firstly, although AKI is a frequent post-operative complication with typical incidences ranging from 20% to 37% in high risk surgery, most of the included RCTs appear to be underpowered (Table 1), with only 904 patients from RCTs summarised in this review. Therefore, there remains a demand for larger, adequately powered studies to examine the pharmacological agents available for AKI prevention.[10]

Secondly, peri-operative renal injury may result from multiple aetiologies. Patient comorbidities,[54] pre-renal fluid status,[8] inflammation,[55] direct ischaemia,[30] ischaemic 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, aetiologies. Nevertheless, in combination with optimal goal directed fluid therapy, mannitol may optimise 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]

Thirdly, careful patient selection may be key for a strategy to prevent AKI. In procedures with a higher risk of post-operative 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 the 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]

Fourthly, measurement of GFRs could be regarded as the gold standard for assessment of renal function. Given that this is impractical for peri-operative use, most investigations use 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 (decreased) 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] 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 few years.[61] Some were tested in studies included in this review (e.g., NGAL, cystatin C, and others).[33,35,37–39] Of these, cystatin C and NGAL might be the most promising. Cystatin C, a 13-kDa protein, is freely filtered, reabsorbed, and metabolised in the proximal tubule.[61,62] Serum cystatin C levels correlate well with GFR, and increased urinary cystatin C excretion reflects AKI as its uptake is reduce by damaged tubules.[61,62] With a cystatin C half life of about one third the half life of creatinine, steady state conditions may be reached faster.[63] 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).[61,62]

Nevertheless, although new biomarkers appear promising, it appears that further research is required before they can be applied in daily clinical use. The matrix of testing, AKI related specificity, and potential confounding medications could influence cut offs and diagnostic value.[61–63]

Limitations to this analysis include the fact that the literature research was deliberately restricted to studies performed after 1990, assuming that surgical technique, anaesthetic management, and study design has evolved in the last 30 years. Furthermore, studies included appear heterogeneous with regard to different mannitol regimens applied, different end points, and different sample sizes. Owing to this heterogeneity, performing a meta-analysis did not seem reasonable.

Moreover, retrospective study of mannitol in partial nephrectomy was found which was published as an abstract only and was therefore not included.[64] 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 peri-operative measure in CPB 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 peri-operative setting in specific indications.

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CONFLICT OF INTEREST

None.

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