Effect of Mannitol on Kidney Function After Kidney Transplantation: A Systematic Review and Meta-Analysis

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ABSTRACT

Background. The effect of mannitol usage during kidney donation and kidney transplantation is still unclear. Therefore, we performed a systematic review and meta-analysis to research the difference in graft function between kidney grafts treated with and without mannitol.

Methods. A literature search was performed in 5 databases and included 8 eligible studies out of 3570 references, which were included up to July 12, 2021. Relevant outcomes for analysis were graft survival, rejection, acute renal failure, delayed graft function, renal failure, creatinine clearance, diuresis, and serum creatinine.

Results. Eight studies were identified, 1 study examining the effect of mannitol during kidney donation and 7 studies during kidney transplantation, of which 6 eligible for meta-analysis. A total of 1143 patients were included in these studies. The following outcome measures demonstrated significant differences in favor of mannitol usage compared with a control group: acute renal failure (risk ratio [RR], 0.45; 95% confidence interval [CI], 0.26−0.79; $P < .01$]) and delayed graft function (RR, 0.25; 95% CI, 0.08−0.77; $P = 0.02$ and RR, 0.69; 95% CI, 0.51−0.94; $P = 0.94$). Differences in other outcome parameters were not significant.

Conclusions. This systematic review and meta-analysis suggested that the use of mannitol during kidney transplantation leads to lower incidence of acute renal failure and delayed graft function. For all other outcomes, no significant difference was found. Further research should be conducted on the use of mannitol during donor nephrectomy because of the limited availability of studies. Finally, for interpretation of the outcomes, the quality of the evidence should be taken into consideration and we emphasize the need for more up-to-date research.

ISCHE mia and reperfusion during kidney transplantation cause endothelial and tubular epithelial cell damage that may lead to acute kidney injury (AKI) and delayed graft function (DGF) [1]. The ischemia-reperfusion injury (IRI) is due to a complex antigen-independent inflammatory process mediated by the innate immune system [2,3].

Studies were conducted to investigate the beneficial effect of mannitol [4-6], a nonabsorbable sugar widely distributed in fruits and vegetables and used in the food industry, for reducing IRI. Mannitol elevates blood plasma osmolality, resulting in enhanced flow of water from tissues. Thus, cerebral edema, elevated intracranial pressure, and cerebrospinal fluid volume and pressure may be reduced. As mannitol is not reabsorbed in the renal tubule and may increase the osmolality of the glomerular filtrate, facilitating excretion of water, it can be used as a diuretic agent [7]. Intraoperative mannitol is routinely administered as a renoprotective solution during kidney transplantation. The role of mannitol as a protective agent is based on the release of intrarenal vasodilating prostaglandins and natriuretic peptides next to its oxygen-free radical scavenger properties. These beneficial characteristics will result in intrarenal vasodilatation and protection of the renal allograft at the time of reperfusion [6-9]. An international survey reported that nearly two-thirds of centers performing high-volume live donor nephrectomy prefer to use mannitol as a kidney protector. However, controversy remains over the benefits of mannitol [10].

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The purpose of this systematic review and meta-analysis was to assess the effect of mannitol during kidney donation and kidney transplantation on graft function.

MATERIALS AND METHODS

Together with the assistance of a clinical librarian, we searched Embase, Medline, Web of Science, Cochrane, and Google Scholar database. The search included the following terms: kidney donation, kidney/renal transplantation, Mannitol (Table 1). The literature search was limited to articles available until July 12, 2021.

Inclusion criteria were studies that focused on either graft survival, rejection, acute renal failure/acute tubular necrosis, DGF, renal failure, creatinine clearance, diuresis, and serum creatinine as outcome measures. Furthermore, randomized controlled trials, prospective cohort studies, and retrospective cohort studies were included. Finally, studies eligible for inclusion had to compare the use of mannitol at the nephrectomy or kidney implantation in kidney transplantation with a solution without mannitol.

We used predefined exclusion criteria: studies focusing on humans <18 years of age, non-English articles, animal studies, combined organ transplants, partial nephrectomies, and specific types of articles (eg, conference abstracts letters to the editor, replies, editorials, case reports, guidelines, and reviews). Furthermore, duplicate articles were removed.

Study Selection, Data Extraction, and Assessment of Study Quality

Eligibility was independently assessed for each study by 2 reviewers (S.C.L. and G.N.S.). First, the articles were assessed for relevance based on title and abstract. The remaining studies were assessed for relevance by evaluation of full-text articles. Conflicting screening outcomes were resolved by consensus. The article was written according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [11].

The data extraction was performed independently by 2 reviewers (S.C.L. and G.N.S.). To assess the quality of the studies, these reviewers performed an independent quality evaluation for the included articles using the appropriated evaluation tool (the Newcastle-Ottawa scale [12] in case of prospective or retrospective studies and the Jaded Scale in case of randomized controlled studies [13]).

Outcomes and Outcome Measurements

The following outcomes were considered for analysis when the comparison was made between with or without the usage of mannitol during donor nephrectomy and kidney transplantation: 1- and 5-year graft survival, creatinine clearance, serum creatinine, acute renal failure (ARF)/acute tubular necrosis, diuresis or urine production, and DGF.

ARF is defined as oliguria from a kidney graft and rising serum creatinine [14], which results in the necessity for dialysis during the postoperative course, with an intact vascular anastomosis and without renal obstruction. DGF was described as the need for a return to dialysis within 1 week after transplantation. A distinction has been made between the use of mannitol during donor nephrectomy and during kidney transplantation.

Table 1. Search Terms Used With the Corresponding Libraries

Embase.com
('kidney transplantation'/exp OR 'kidney donor'/de OR 'kidney preservation'/exp OR 'nephrectomy'/exp OR 'renal graft dysfunction'/exp OR 'organ transplantation'/de OR (((kidney* OR renal OR organ OR organs) NEAR/10 (transplant* OR graft* OR allograft* OR xenograft* OR homograft OR allotransplant* OR autotransplant* OR xenotransplant* OR homotransplant OR donor* OR donation* OR recipient* OR cadaver* OR preservat* OR storage* OR warm-ischem* OR warm-ischaem* OR cold-ischem* OR cold-ischaem*)) OR nephrectom* OR uninephrectom*):ab,ti) AND ('mannitol'/exp OR (acrosmosol OR aridol OR bronchitol OR mannit* OR osmitrol OR osmofundin OR osmosal OR osmosteril OR pearlitol OR resectisol):ab,ti)
Medline Ovid
("kidney transplantation"/ OR kidney/tr OR "nephrectomy"/ OR "organ transplantation"/ OR (((kidney* OR renal OR organ OR organs) ADJ10 (transplant* OR graft* OR allograft* OR xenograft* OR homograft OR allotransplant* OR autotransplant* OR xenotransplant* OR homotransplant OR donor* OR donation* OR recipient* OR cadaver* OR preservat* OR storage* OR warm-ischem* OR warm-ischaem* OR cold-ischem* OR cold-ischaem*)) OR nephrectom* OR uninephrectom*).ab,ti,kf.) AND ("mannitol"/ OR (acrosmosol OR aridol OR bronchitol OR mannit* OR osmitrol OR osmofundin OR osmosal OR osmosteril OR pearlitol OR resectisol).ab,ti,kf.)
Cochrane CENTRAL
((((kidney* OR renal OR organ OR organs) NEAR/10 (transplant* OR graft* OR allograft* OR xenograft* OR homograft OR allotransplant* OR autotransplant* OR xenotransplant* OR homotransplant OR donor* OR donation* OR recipient* OR cadaver* OR preservat* OR storage* OR warm-ischem* OR warm-ischaem* OR cold-ischem* OR cold-ischaem*)) OR nephrectom* OR uninephrectom*):ab,ti) AND ((acrosmosol OR aridol OR bronchitol OR mannit* OR osmitrol OR osmofundin OR osmosal OR osmosteril OR pearlitol OR resectisol):ab,ti)
Web of science
TS=((((kidney* OR renal OR organ OR organs) NEAR/9 (transplant* OR graft* OR allograft* OR xenograft* OR homograft OR allotransplant* OR autotransplant* OR xenotransplant* OR homotransplant OR donor* OR donation* OR recipient* OR cadaver* OR preservat* OR storage* OR warm-ischem* OR warm-ischaem* OR cold-ischem* OR cold-ischaem*)) OR nephrectom* OR uninephrectom*)) AND ((acrosmosol OR aridol OR bronchitol OR mannit* OR osmitrol OR osmofundin OR osmosal OR osmosteril OR pearlitol OR resectisol)))
Google scholar
"kidney|renal|organ transplantation|transplant|graft|allograft|xenograft|homograft|allotransplant|autotransplant|xenotransplant|homotransplant|donor|donorsidonation|recipient|recipients" mannitol

Statistical analysis

This meta-analysis was performed in line with recommendations from the Cochrane Collaboration and Meta-analysis of Observable Studies in Epidemiologic guidelines [15]. A random-effects model was used because of anticipated heterogeneity between the included studies and used the Mantel−Haenszel method due to relatively small population numbers. Potential variance due to heterogeneity between studies was estimated by the statistic I^2 which was defined as the following: might not be important (<40%), moderate heterogeneity (30%-60%), may represent substantial heterogeneity (50%-90%), or is considerable heterogeneity (>75%). If ≤3 studies were included for a meta-analysis outcome, a descriptive analysis was used. $P < .05$ was considered statistically significant. If a forest plot was applied to assess the overall risk ratio or standardized mean difference, a sensitivity analysis (leave-one-out analysis) was conducted to estimate the individual effect on the outcome.

For a dichotomous outcome (e.g., graft survival), we used risk ratio as the method to estimate the probability of the outcome in the mannitol group compared with the control group. When the outcome was continuous, the standard mean difference was used to measure the effect size. Statistical analysis was performed using RevMan 5.3 Cochrane software (Cochrane UK, Oxford, United Kingdom).

Ethics Statement

The present study did not require approval from an ethics board and was therefore exempt from approval.

RESULTS

The literature search resulted in 3570 studies, of which 8 met our inclusion criteria [8,9,16-21]. These 8 studies were used to extract data for qualitative synthesis and resulted in 1143 included patients (Fig 1). The characteristics of each study are presented in Table 2. One study examined the effect of mannitol during donor nephrectomy and 7 studies during kidney transplantation. Six studies were included in the meta-analysis because they included outcomes that were eligible for inclusion in a meta-analysis [8,9,16,18-20]. Koning et al [17] and Esfahani et al [21] did not include any outcomes that were eligible for the meta-analysis.

Mannitol used during donor nephrectomy

In 1 of the 8 included articles [21], mannitol was administered during the donor nephrectomy. In this randomized clinical trial, 60 donors were assigned in 2 equally split groups that received mannitol during donor nephrectomy (intervention group) or not (control group). Urine volume at the first 24 hours after surgery was 8575.86 ± 7282.05 mL in the mannitol group and 9903.33 ± 8242.23 mL in the control group ($P = .285$). In repeated measurements on 10 consecutive days, the blood urea nitrogen difference between the 2 groups was not significant ($P = .552$). On repeated measures of creatinine on consecutive days, however, the difference between the 2 groups was not significant ($P = .584$).

Mannitol used during kidney transplantation

Seven of 8 studies evaluated the use of mannitol during kidney implantation [8,9,16-20]. In all, 1051 patients were included from these studies. One study was not eligible to include in the meta-analysis [17] because its only outcome variable provided was DGF and only 1 one other study included this outcome variable.

Graft survival

One study [9] reported graft survival with 131 patients. Van Valenberg et al [9] compared mannitol vs glucose in 2 arms. In the first arm, patients received azathioprine as an immunosuppressive, and in the second arm, the patients received cyclosporine. The azathioprine arm showed a 1-year survival probability of 70.5% for mannitol and 80.3% for glucose, with a risk ratio (RR) of 1.47 (95% confidence interval [CI], 0.64−3.41; $P = .5$). In the cyclosporine arm, a 1-year survival probability of 81.6% vs 87.8% was found (RR, 1.50; 95% CI, 0.47−4.82; $P = .37$) (Table 3).

Rejection

Tiggeler et al [8] and Griño et al [16] included rejection as their outcome measures with 90 patients. The first article found that patients on restrictive hydration + mannitol vs restrictive hydration have lower 3-month rejection rates, videlicet 63.2% vs 75% (RR, 0.30; 95% CI, 0.09−1.04; $P = 0.06$.

Griño et al found a 21% rejection rate in mannitol vs 48% in Euro-Collins solution, which showed a risk ratio of 0.69 (95% CI, 0.18−0.59; $P = .58$) (Table 3).

Delayed graft function

Two of 7 studies (17,19) used DGF as an outcome measure. These studies included 569 patients. Weimar et al [19] (N = 44) found a DGF incidence of 14% in mannitol and 55% in control (saline), which resulted in a RR of 0.25 (95% CI, 0.08−0.77; $P = .02$).

Koning et al (N = 525) found a DGF incidence of 21% in mannitol and 30% in control, with a RR of 0.69 (95% CI, 0.51−94; $P = 0.03$; Table 3).

Acute Renal Failure

Five [8,9,16,18,19] included acute tubular necrosis or ARF in their studies and included 505 patients. All studies included renal failure within 3 months, but van Valenberg et al [9] included the occurrence of ARF up to 1 year (Table 3).

Van Valenberg et al [9] found that in the azathioprine and cyclosporine arms, a mannitol solution led to less ARF. In the azathioprine arm, 18% of the patients in the mannitol group and 44% in the glucose group ended up with ARF (RR, 0.41; 95% CI, 0.18−0.93; $P = 0.03$). In the cyclosporine arm, 19% and 53% in the mannitol and glucose groups, respectively, ended up with ARF (RR, 0.35; 95% CI, 0.16−0.78; $P = .01$). Griño et al found that patients treated with mannitol had less chance of acquiring renal failure (13%) than patients receiving Euro-Collins solution (77%; RR, 0.17; 95% CI, 0.06−0.49; $P = .001$. Weimar et al [19] found that 3 patients in the mannitol group

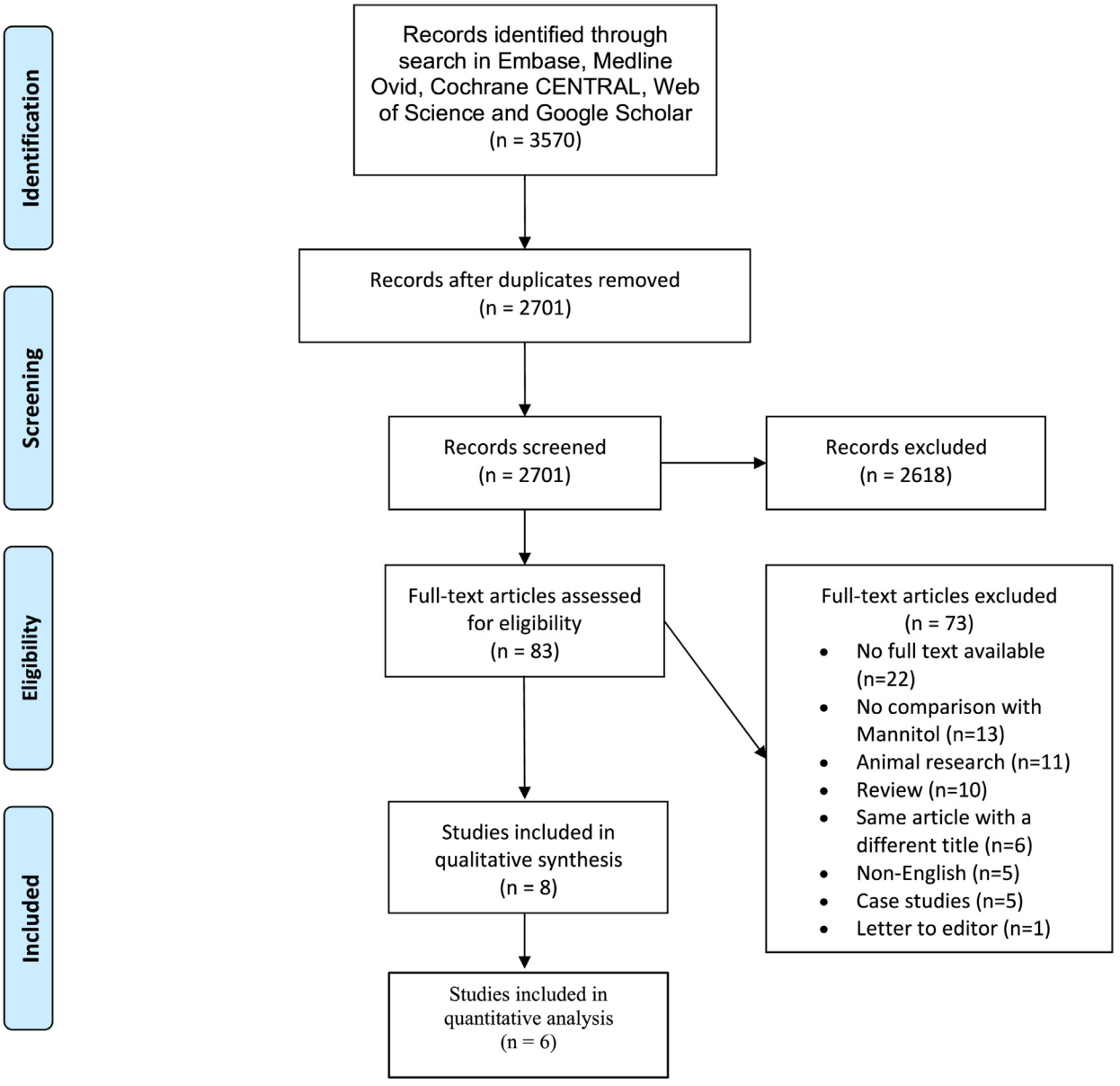

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Fig 1. Selection of studies.

Table 2. Baseline Characteristics, Study Outcome Measurements, and Study Quality Assessment Scores

	Year of Publication	Study Design (trial)	ntervention (n)	Control (n)	Total Patients	Follow-Up	Study Outcomes	Quality Assessment
Donor								
Esfahani et al [21]	2014	Randomized clinical	Mannitol (30)	No-mannitol (30)	60	10 d	pH, BUN, sCr	Medium
Recipient								
Griño et al [16]	1987	Retrospective	Mannitol 3.5/100 mL (23)	Euro-Collins (27)	50	6 mo	sCr, ARF, diuresis, RE	Medium
Koning et al [17]	1997	Prospective	Mannitol + UW + possibly furosemide (367)	UW + possibly furosemide (158)	525	48 mo	GF	High
Reiterer et al [20]	2020	Randomized clinical	Mannitol 20% of 5 mL/kg (17)	0.9% NaCl of 5 mL/kg (17)	32	1 d	Diuresis, sCr	High
Tiggeler et al [8]	1985	Prospective	Mannitol 20% 250 mL + restricted fluid (19)/moderate hydration (21)	Restricted fluid infusion (21)	61	3 mo	Diuresis, sCr, ATN, HD, HK, RE	High
Salahi et al [18]	1995	Retrospective	Mannitol 20% 250 mL (139)	Moderate hydration (101)	240	-	sCr, diuresis, ATN	Low
van Valenberg et al [9]	1987	Randomized prospective	Aza + Mannitol 20% 250 mL (33) Cyclo + Mannitol 20% 250 mL (65)	Aza + glucose (34) Cyclo + glucose (32)	131	12 mo	ARF, GS, diuresis	Medium
Weimar et al [19]	1983	Randomized prospective	Mannitol 20% 250 mL (22)	Saline (22)	44	12 mo	IRF, sCr, ATN, HD	Medium

ARF, acute renal failure; ATN, acute tubular necrosis; Aza, azathioprine; BUN, blood urea nitrogen; Cyclo, cyclosporine; GF, graft failure; GS, graft survival; HD, hemodialysis; HK, hyperkaliemia; IRF, immediate renal function; RE, rejection; sCr, serum creatinine; UW, University of Wisconsin fluid.

(13.6%) and 12 patients in the saline group (54.5%) had to receive dialysis treatment because of ARF. This resulted in a RR of 0.25 (95% CI, 0.08−0.77; P = .02). Tiggeler et al [8] found that mannitol was associated with a higher ARF incidence compared with restricted hydration. The probability of ARF was 53% in the mannitol group and 43% in controls (RR, 1.23; 95% CI, 0.64−2.36; P = .54). The study by Salahi et al [18] showed a probability of ARF of 17.5% in the mannitol and 25.7% in the control group (RR, 0.64; 95% CI, 0.39−0.77; P =.08). These studies are shown in a forest plot (Fig 2) with a combined RR of 0.45 (95% CI, 0.26−0.79; P = .005). The heterogeneity shows an I^2 of 67% with = P = 0.01, thus heterogeneity is considered significant.

Serum Creatinine

Four [8,9,16,20] of 7 studies that included 186 patients discussed creatinine serum. Van Valenberg et al [9] was the only study to look at day 3 after transplantation, whereas Tiggeler et al [8] and Griño et al [16] measured the serum creatinine at month 3 after transplantation. The first resulted in a mean serum creatinine of 360 μmol/L (standard deviation [SD] = 210) vs 580 μmol/L (SD = 270), standard mean difference (SMD) was −0.90 (95% CI, −1.41 to 0.38; P < .001). The second study, respectively, gave a serum creatinine of 145 μmol/L (SD = 34.6) in the mannitol group vs 99.7 μmol/L (SD = 40.7) in the restricted hydration group (SMD, 0.34; 95% CI, −0.28 to 0.97; P = .29). In the last study by Griño et al a mean serum creatinine of 145 μmol/L (SD = 40) was found in the mannitol group vs 203 μmol/L (SD = 94) in the control group (SMD, −1.36; 95% CI, −1.98 to −0.74; P < .0001) (Table 4). Reiterer et al [20] showed that serum creatinine did not differ between mannitol 451 μmol/L (SD = 221) and placebo 504 μmol/L (SD = 186; P = .384) (Table 4).

The meta-analysis shows a SMD of −0.36 (95% CI, −1.02 to 0.30; P = .28). The heterogeneity shows an I^2 = 83% with P = .28 and this forest plot suggests therefore considerable heterogeneity (Fig 3).

Diuresis

In 3 studies [8,16,20], the diuresis or urine production was measured on the first day after transplantation. Tiggeler et al [8] found that the mean diuresis production was not significantly higher in mannitol groups compared with restricted hydration, 102 mL/h (SD = 108) vs 60 mL/h (SD = 52; SMD, 0.49; 95% CI, −0.14 to 1.12; P = .13). Griño et al showed that the diuresis was significantly higher in the mannitol group with 244 mL/h (SD = 143) compared with 83 mL/h (SD = 93) in the patients who received Euro-Collins. The SMD in the present study was 1.34 (95% CI, 0.72−1.96; P < .0001). Reiterer et al [20] showed a median diuresis of 1600 (25^{th}-75^{th} percentile: 690−2750) in patients treated with mannitol, whereas those who received placebo showed a median diuresis of 1125 (25^{th}-75^{th} percentile: 550 −2375) (Table 4).

Table 3. Summary of Findings for the Use of Mannitol in Kidney Transplantation: Only Dichotomous Outcomes

			No. of Patients Included (Mannitol vs Control)	Measured at Time . . .	Percentage of Population With an Event (Mannitol vs Control)	Risk Ratio [95% CI], *P* (Mannitol vs Control)
Graft survival	Van Valenberg et al [9]	Azathio-prine	33 vs 34	1 y	70.5% vs 80.3%	1.47 [0.64−3.41] $P = 0.5^{ns}$
		Cyclo-sporine	32. vs 32	1 y	81.6% vs 87.8%	1.50 [0.47−4.82] $P = 0.37^{ns}$
Rejection	Griño et al [16]		19 vs 21	3 mo	63.2% vs 75%	0.30 [0.09−1.04] $P = 0.06^{ns}$
	Tiggeler et al [8]		23 vs 27	6 mo	21% vs 48%	0.69 [0.18−2.59] $P = 0.58^{ns}$
DGF	Weimar et al [19]		22 vs 22	Within first week	13.6% vs 54.5%	0.25 [0.08−0.77] $P = 0.02^{*}$
	Koning et al [17]		367 vs 158	Within first week	21% vs 30%	0.69 [0.51−0.94] $P = 0.03^{*}$
ARF	Van Valenberg et al [9]	Azathio-prine	33 vs 34	1 y	18% vs 44%	0.41 [0.18, 0.93] $P = 0.03^{*}$
		Cyclo-sporine	32 vs 32	1 y	19% vs 53%	0.35 [0.16, 0.78] $P < 0.01^{\dagger}$
	Griño et al [16]		23 vs 27	3 mo	13% vs 77.8%	0.17 [0.06−0.49] $P < 0.001^{\ddagger}$
	Weimar et al [19]		22 vs 22	3 mo	13.6% vs 54.5%	0.25 [0.08, 0.77] $P = 0.02^{*}$
	Tiggeler et al [8]		19 vs 21	mo	53% vs 43%	1.23 [0.64−2.36] $P = 0.54^{ns}$
	Salahi et al [18]		139 vs 101	3 mo	17.5% vs 25.7%	0.64 [0.39−0.77] $P = 0.08^{ns}$

ARF, acute renal failure; CI, confidence interval; DGF, delayed graft function; ns, non significant.
* $p < 0.05$.$^{\dagger}p < 0.01$.$^{\ddagger}p < 0.001$.

Creatinine Clearance

Two studies [18,19] with 264 patients measured creatinine clearance. Weimar et al [19] found that mannitol, compared with saline, resulted in a creatinine clearance on day 3 after transplantation of 43 mL/min (range, 6−104) vs 25 mL/min (range, 10−80). Salahi et al [18] found that a mannitol + moderate hydration solution compared with moderate hydration resulted in an improvement of 47 vs 30 mL/min on day 14 in related donor kidney transplantation. On the same day, an improvement was seen in the nonrelated kidney transplantation group of 52 vs 40 mL/min. Both in favor of mannitol (Table 4).

Because no SD or CI was provided, it was not possible to calculate the statistical significance and to provide a defined conclusion about these results.

The Newcastle-Ottawa scale (NOS) and Jadad score results are shown in Tables 5 and 6 for the quality evaluation of the included studies. The overall NOS score is medium and is used for all the nonrandomized studies. The overall Jadad score is medium and used to assess the quality of randomized studies.

DISCUSSION

The present systematic review demonstrated that the effect of mannitol during live donor nephrectomy and kidney transplantation has no significant improvement on renal function after kidney transplantation, except for a significant effect on DGF and ARF in favor of mannitol.

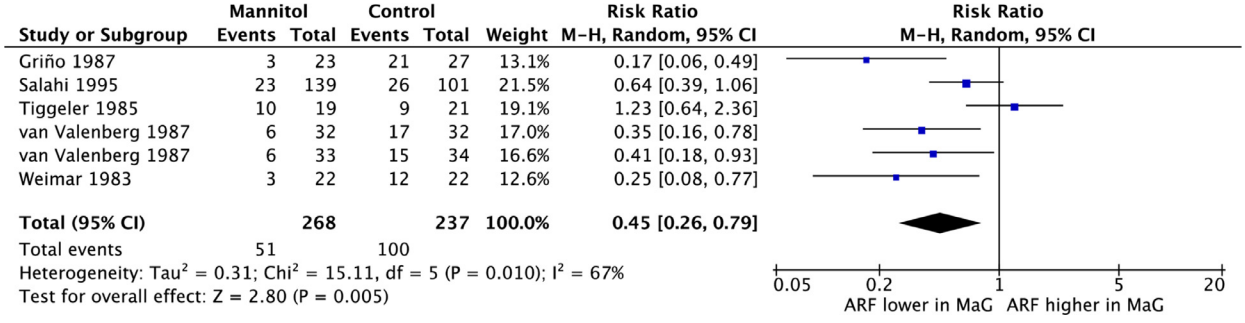

Fig 2. Mannitol vs control group. Outcome: acute renal failure. ARF, acute renal failure; MaG, mannitol group.

Table 4. Summary of Findings for Use of Mannitol in Kidney Transplantation: Continuous Outcomes Only

		Patients Included (Mannitol vs Control)	Measured at Time . . .	sCr mean in μmol/L (SD)CrCl in mL/min (Range) (Mannitol vs Control)	SMD [95% CI], *P*(Mannitol vs Control)
sCr	Van Valenberg et al [9]	32 vs 32	Day 3	360 μmol/L (210) vs 580 μmol/L (270)	−0.90 [−1.41 to 0.38]; $P < .001^{*}$
	Tiggeler et al [8]	19 vs 21	Month 3	112.9 μmol/L (34.6) vs 99.7 μmol/L (40)	0.34 [−0.28 to 0.97]; $P = 0.29^{ns}$
	Griño et al [16]	23 vs 27	Month 3	173 μmol/L (74) vs 492 μmol/L (307)	−1.36 [−1.98 to −0.74]; $P < .0001^{\dagger}$
	Reiterer et al [20]	16 vs 16	24 h	46 μmol/L (22) vs 50 μmol/L (19)	−0.19 [−0.88 to 0.51]; $P = 0.678$
Diuresis	Tiggeler et al [8]	19 vs 21	First 24 h	102 (108) vs 60 (52)	0.49 [−0.14 to 1.12]; $P = 0.13^{ns}$
	Griño et al [16]	23 vs 27	First 24 h	244 (143) vs 83 (93)	1.34 [0.72−1.96]; $P < .0001^{\dagger}$
	Reiterer et al [20]	16 vs 16	First 24 h	1600 [690−2750] vs 1125 [550−2375]	$P = .678^{ns}$
CrCl	Weimar et al [19]	22 vs 22	Day 3	43 mL/min (6−104) vs 25 mL/min (10−80)	
	Salahi et al [18]	139 vs 101	Day 14	47 mL/min vs 30 mL/min	

CrCl, creatinine clearance; ns, non-significant; sCr, serum creatinine; SD, standard deviation; SMD, standard mean difference.
*$p < 0.05$.
†$p < 0.01$.

In the clinical setting, mannitol is often administered to patients who undergo a live donor nephrectomy and/or kidney transplantation [10,22]. In an online questionnaire sent to 40 kidney transplant surgeons in the United Kingdom, Hanif et al [22] explored their practice of kidney transplantation with or without intraoperative diuretics. Twenty-one of the surgeons reported using mannitol as an intraoperative diuretic. There was no significant difference in 1-year graft survival between the patients transplanted with or without intraoperative diuretics (94% and 94%, respectively, $P = .08$) as well as the incidence of DGF (16 of 69, 23% and 21 of 80, 26%, respectively; $P = 0.07$). Cosentino et al [10] performed an international survey among high-volume tertiary centers. Of centers performing high-volume live donor nephrectomy, 64% prefer to use mannitol as a kidney protector, without reporting the outcome after kidney transplantation. Three more recently published studies and guidelines address the problem that mannitol is still administered routinely [20,23,24].

The beneficial effects of mannitol administration in patients at risk for AKI have been studied in a recent systematic review [25]. Nine trials were included with 626 patients. The use of mannitol for prevention of AKI in high-risk patients could not reduce the serum creatinine level (mean difference = 1.63; 95% CI, 26.02−9.28) as well as the incidence of ARF or the need for dialysis (RR, 0.29; 95% CI, 0.01−6.60). The level of serum creatinine was negatively affected by the use of mannitol in patients undergoing radiocontrast agents injection.

Mannitol, like any drug, has adverse effects that should be taken into consideration and prophylactic mannitol may be associated with significant toxicity. The initial volume expansion of mannitol can provoke heart failure and pulmonary congestion. The increased intravascular volume is quickly compensated with a diuretic effect that may cause hypovolemia. This increased urinary output may cause fluid and electrolyte imbalance such as metabolic acidosis, hypokalemia, and hypernatremia. In large doses, it can also cause renal failure because of intrarenal vasoconstriction and intravascular volume depletion [7,26,27]. A rare adverse effect is mannitol-induced nephrosis. A study by Dickenmann et al [28] concluded that in patients with preexisting kidney disease, small doses (~300 g) can precipitate kidney failure. This study also pointed out that preexisting impaired kidney function, comedication with

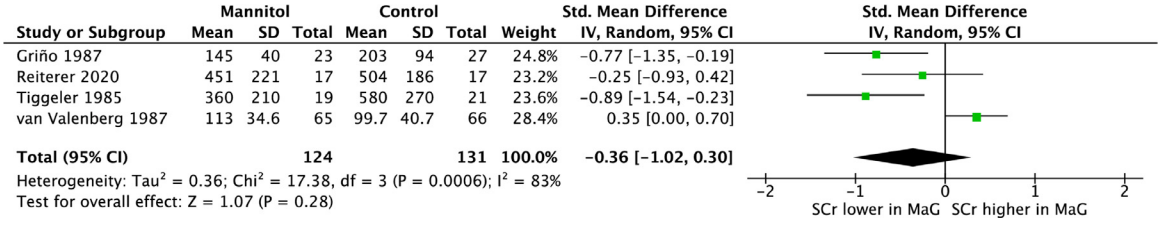

Fig 3. Mannitol vs control group. outcome: serum creatinine. MaG, mannitol group; Scr, serum creatinine.

Table 5. Quality Assessment of Nonrandomized Trials Regarding Newcastle-Ottawa Score*

	Selections				Comparability		Outcome Assessment			Score	Quality
	Representativeness 1	Selection non-exposed cohort 2	Ascertainment exposure 3	Outcome absent at start 4	Controls for primary factor 5	Controls for additional factor 6	Assessment of outcome 7	Follow-up length 8	Adequate follow up 9		
Griño et al [16] 1987	-	•	-	•	•	-	-	•	•	5	Medium
Koning et al [17] 1997	•	•	•	•	•	•	•	•	•	9	High
Tiggeler et al [8] 1985	•	•	•	•	•	•	-	•	•	**8**	High
Salahi et al [18] 1995	•	-	-	-	-	-	-	-	-	**1**	Low
Van Valenberg et al [9] 1987	•	•	•	•	•	-	-	-	-	**5**	Medium

* 0 to 4 points = low score; 5 to 7 = medium score; and >7 points = high score.

Table 6. Quality Assessment of Randomized Trials Regarding the Jadad Score

	Points	Weimar et al [19] 1983	Esfahani et al [21] 2014	Reiterer et al [20] 2020
1.	Was the study described as randomized?	+ 1	+ 1	+1
2.	Was the method used to generate the sequence of randomization described and appropriate (table of random numbers, computer-generated, etc)?	-	+ 1	+1
3.	Was the study described as double-blind?	-	+ 1	+1
4.	Was the method of double-blinding described and appropriate (identical placebo, active placebo, dummy, etc)?	-	+ 1	+1
5.	Was there a description of withdrawals and dropouts?	-	-	+1
6.	Deduct 1 point if the method used to generate the sequence of randomization was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc)	-	- 1	-
7.	Deduct 1 point if the study was described as double-blind but the method of blinding was inappropriate (eg, comparison of tablet vs injection with no double dummy)	-	- 1	-
	Result:	**1**	**2**	**5**

furosemide, and kidney transplantation (including therapy with cyclosporine) are independent risk factors for developing AKI.

When looking at the present results, we concluded that mannitol significantly decreases ARF after kidney transplantation. We found substantial heterogeneity in the forest plot, but when we combine these findings with the sensitivity analysis, we concluded that this is mainly caused by the outlying results of Tiggeler et al [8]. When the study of Tiggeler et al was excluded from analysis, the I^2 decreased to 40% with $P = .15$. Furthermore, we found that graft function was significantly higher in the group treated with mannitol than in those patients treated with glucose, as seen in all included studies. Not all other variables led to a significant result.

Finally, we observed a trend in serum creatinine and diuresis as being benefited by mannitol compared with the control group during kidney transplantation. Two [9,16] of 4 studies showed a highly significant lower serum creatinine in patients who received mannitol and 2 studies did not find a significant difference [8,20]. Regarding diuresis, only 1 study showed a significant improvement for mannitol [16].

Limitations

All studies included in the systematic review, except those by Esfahani et al and Reiterer et al [20], were published before 2000, and many scored low or medium on the NOS/Jadad

Table 7. Extended Study Characteristics Discussing Population Age, ECD, Immunosuppression, and the Type of Donor

	Year of Publication	Age Donor	ECD Donor age >60 y	Donor Age >50 y With Criteria	Immunosuppression	Deceased/ Living Donor
Donor						
Esfahani et al [21]	2014	18-55 (range)	0%	NR	NR	Living
Recipient						
Griño et al [16]	1987	Mannitol: 28 ±13 Control (ECD): 36 ±15 (mean ± SD)	NR	NR	Cyclosporine, prednisone	Deceased
Koning et al [17]	1997	96% ≤50 y	NR	NR	Dexamethasone (UW), cyclosporine, variable rejection therapy	Deceased
Reiterer et al [20]	2020	Mannitol: 62 [57−71] Placebo: 53 [45−68] median [25th, 75th percentile]	NR	NR	NR	Deceased
Tiggeler et al [8]	1985	Group 1 (control): 27.8 ± 14.1 Group 2: 28.5 ± 17.4 Group 3: 28.2 ± 12.8 (mean ± SD)	NR	NR	Prednisone, azathioprine	Deceased
Salahi et al [18]	1995	NR	NR	NR	NR	Deceased
van Valenberg et al [9]	1987	NR azathioprine + prednisone Group 2: cyclosporine + prednisone	NR Deceased	NR	Group 1:	
Weimar et al [19]	1983	Mannitol: 21.5 (7−47) Control: 20.5 (0−56) (median, range)	0%	NR	NR	Deceased

ECD, extended criteria donor; NR, not reported; SD, standard deviation; UW, University of Wisconsin solution.

quality score. This phenomenon that evidence-based medicine must rely on less recent evidence, is often seen in the literature. Addressing the potential bias, time-dependent efficacy and quality differences are key next to the fact that older data should be interpreted with caution [29]. For instance, the immunosuppression doses, cold ischemia times, and kidney transplantation protocols in the included studies published before 2000 are different than the ones used in 2021. Therefore, we should question the findings that administering mannitol during kidney transplantation is beneficial in terms of DGF and

Table 8. Extended Study Characteristics Discussing DM and Cause of Death of Donor, Recipient Weight, sCr, and Hypertension in Recipient*

	DM	Cause of Death	Weight	sCR	Hypertension/SBP
Donor					
Esfahani et al [21]	NR	NR	NR	NR	NR
Recipient					
Griño et al [16]	NR	NR	NR	Mannitol: 105 ±30 Control (ECD): 103 ±31 (mean ± SD)	NR
Koning et al [17]	0%	Reported	70 (30-85), median, range	80 (mean, 95% CI 44-140)	0%
Reiterer et al [20]	31% & 6%	NR	74 ± 17 vs 78 ± 17	7.5 [5.5, 8.7] vs 8.3 [5.5, 9.8]	94% vs 94%
Tiggeler et al [8]	NR	NR	NR	Group 1 (control): 102.3 ± 32.9 Group 2: 90.3 ± 33.2 Group 3: 104.1 ± 29.6 (mean ± SD)	Group 1 (control): 114 ±20 Group 2: 106 ± 19 Group 3: 113 ± 22 (mean ± SD) SBP
Salahi et al [18]	NR	NR	NR	NR	NR
van Valenberg et al [9]	NR	NR	NR	Group 1 Mannitol: 97 ± 30 Glucose: 98 ± 41 Group 2 Mannitol: 96 ± 34 Glucose: 90 ± 30 (mean ± SD)	Group 1 Mannitol: 116 ± 18 Glucose: 116 ± 16 Group 2 Mannitol: 117 ± 22 Glucose: 123 ± 20 (mean ± SD) SBP
Weimar et al [19]	NR	NR	NR	Mannitol: 119 (70-186) Control: 85 (18-241) (median, range)	NR

DM, diabetes mellitus; ECD, extended criteria donors; NR, not reported; SBP, systolic blood pressure; sCr, serum creatinine; SD, standard deviation.

* No study reported hepatitis C virus status or ethnicity. These results are therefore omitted from this table.

ARF because it is uncertain if these results still hold in studies with up-to-date protocols. Another important limitation becomes apparent when looking at Tables 7 and 8, which show that included studies often do not provide complete information about their populations (eg, concerning extended criteria donors; cause of death and body mass index are not reported in most studies; however, these variables are needed to assess the bias on a baseline characteristic level). Moreover, the number of patients included in the studies are limited. To achieve a clearer and more solid effect of the intervention, we recommend that future mannitol studies include a larger sample size and be determined to perform multiple center studies.

Two trials described themselves as "randomized" but did not report the method of randomization, which made them less reliable [9,19]. Further research should be conducted on the use of mannitol during donor nephrectomy because the evidence was limited to 1 study [21] performing research on this subject making it impossible to draw conclusions.

Unfortunately, most of our outcome measures of interest were not eligible for quantitative analysis. However, as stated in the methodology section, we argue that the use of a meta-analysis for no more than 3 studies is irrelevant and statistically incorrect, which makes this study and its methodology the highest evidence available regarding the use of mannitol during donor nephrectomy or kidney transplantation.

We used the NOS to assess the quality of included studies. Although some studies described its weaknesses, including low interrater reliability and "uncertain validity" of some items, the NOS appears to be the most popular choice of all the non-randomized study tools and is considered easy to use [30-33].

CONCLUSIONS

This systematic review and meta-analysis suggested that the use of mannitol during kidney transplantation leads to decreased incidence of ARF and DGF. For all other outcomes, no significant difference was found and therefore no evidence that mannitol administered during kidney transplantation is beneficial for the patient. Further research should be conducted on the use of mannitol during donor nephrectomy because of the limited availability of studies. Finally, for interpretation of the outcomes, the quality of the evidence should be taken into consideration, and we emphasize on the need for more up-to-date research.

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