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Preservation Solutions for Static Cold Storage of Kidney Allografts: A Systematic Review and Meta-Analysis

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Static cold storage is the most prevalent method for renal allograft preservation. Several solutions have been designed to counteract the detrimental effects of cold ischemia and reperfusion. The aim of this study was to appraise the evidence for the currently available preservation solutions. We performed a systematic literature search using MEDLINE, EMBASE, the Cochrane Library, the Transplant Library and trial registries. Inclusion criteria specified any comparative, prospective study for deceased donor renal allografts. Studies were assessed for methodological quality. The primary outcome was delayed graft function (DGF). Fifteen trials with a total of 3584 kidneys were included. Eurocollins was associated with a higher risk of DGF than University of Wisconsin solution (UW) in two randomized controlled trials (RCTs) and histidine–tryptophan–ketoglutarate (HTK) in two RCTs. UW was associated with an equal risk of DGF compared with Celsior in three RCTs and HTK in two RCTs. There was limited data regarding other comparisons and outcomes. The choice of preservation solution has an effect on the incidence of DGF, which might, in turn, affect long-term outcomes. Both UW and HTK have lower rates of DGF than Eurocollins. There is no difference in the incidence of DGF with the use of Celsior, HTK and UW. These findings are supported by registry data.

Key words: Kidney transplantation, organ preservation, transplantation, systematic review

Abbreviations: CI, confidence interval; Chi^2, Chi^2 test for heterogeneity, unless otherwise specified; ATG, antithymocyte globulin; Aza, azathioprine; CsA, cyclosporine; EC, Eurocollins solution; CIT, cold ischemic time; CTS, Collaborative Transplant Study; DBD, donation after brain death; DCD, donation after cardiac death; DGF, delayed graft function; HOC, hyperosmolar citrate, Marshall's solution; HR, hazard ratio; HTK, histidine–tryptophan–ketoglutarate, Bretschneider solution; I^2, I^2 test for heterogeneity; ICTRP, International Clinical Trials Registry Platform; IGL-1, Institut Georges Lopez-1 Solution; ITT, intention to treat; MMF, mychophenolate mofetil; Non-RCT, non-randomized controlled trial; NR, not reported; OKT, muromonab; PBS, phosphate buffered sucrose; Pred, prednisolone; Rap, Rapamycin; RCT, randomized controlled trial; RR, relative risk; Tac, tacrolimus; UNOS, United Network for Organ Sharing; UW, University of Wisconsin solution.

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Introduction

The preservation of kidney allografts allows the transport and sharing of organs between centers to improve histocompatibility matches and also allows transplantation to take place on a less urgent basis. Immune induction and maintenance immunosuppressive regimens have advanced considerably in recent years, as has the understanding of allograft rejection, yet organ preservation persists in its most simple form; static cold storage remains the mainstay of preservation for kidney allografts worldwide (1). Numerous preservation solutions have been developed to counteract the detrimental effects of the recovery process, graft cooling and reperfusion. They have been designed to specifically target the biochemical and structural changes that occur during this process, yet vary considerably in the exact nature and concentration of their constituents (2).

Registry data from national and international databases of deceased donor kidney transplants suggests that the choice of preservation solution can affect both the short- and long-term outcomes of the graft (1,3). Of particular interest is the time for the kidney to provide adequate renal function, negating the need for dialysis, the primary purpose of the transplant. This has implications for the risk of acute rejection, long-term graft survival and the cost-effectiveness of the transplant (4,5).

A number of prospective trials have investigated the effect of preservation solution on renal transplant outcomes

over many years, with variable results. Such trials are often underpowered to identify differences in important outcomes, such as delayed graft function (DGF). Two previous systematic reviews have attempted to explore these differences but did not include all preservation solutions. One review included only comparisons of Celsior, University of Wisconsin solution (UW) and hyperosmolar citrate (Marshall's solution, HOC; Ref. 5) whereas the other considered only comparisons of UW with histidine–tryptophan–ketoglutarate (HTK; Ref. 6).

Hypothermic machine perfusion for renal allografts using a new generation of pumps has been the subject of recent studies (7,8), but the evidence for the superiority of machine preservation over static cold storage remains uncertain. This warranted a systematic appraisal of the evidence supporting the use of current preservation solutions.

Materials and Methods

Literature search and inclusion criteria

A systematic literature search was performed using MEDLINE and EMBASE, the Cochrane Library, the Transplant Library of randomized controlled trials (RCTs) from the Centre for Evidence in Transplantation and the International Clinical Trials Registry Platform (ICTRP). Searches were conducted using MeSH and EMTREE keywords with free-text aliases for preservation solutions to capture all relevant references. MEDLINE was searched from 1948 and EMBASE from 1980 to the current date. No language limits were applied. References of included studies, citing articles of included studies and reviews were studied for further potentially relevant references. The final date for literature searches was July 20, 2011.

Inclusion criteria specified any prospective, comparative study of preservation solution for static cold storage of deceased donor renal allografts from any class of adult or pediatric donor. First and subsequent transplants were included. All kidneys were stored by static cold storage alone. Retrospective, animal, noncomparative and/or live donor studies were excluded. Abstracts for inclusion were reviewed by two authors (J.M.O. and S.R.K.) and differences agreed by discussion.

Outcomes

The primary outcome was the rate of DGF, defined as a requirement for dialysis in the first week posttransplantation, and included kidneys that never functioned (primary nonfunction [PNF]). However, the definition of DGF varied between studies; the most used definition was the need for dialysis in the first week, but it was also defined as a need for multiple sessions of dialysis in the first week or a lack of immediate urine production. Despite such differences, the underlying effect should be the same and we have used the definition provided in the original paper. Secondary outcomes were PNF, graft survival, renal function (serum creatinine), biopsy proven acute rejection and patient survival.

Data extraction

Studies are referred to throughout this paper by the first author and year of the earliest peer-reviewed publication. Demographic, quality and outcome data were independently extracted from the included studies into a predesigned Microsoft Excel spreadsheet by two authors (J.M.O. and R.D.M.). Data was taken from all papers describing the study; in the case of discrepancies the most comprehensive paper was used. Any discrepancies in data extraction were settled by discussion and consultation with P.J.M. and S.R.K.

Quality assessment

RCTs were assessed first using the Jadad score, a 0–5 scale dependent upon adequate descriptions of randomization method, blinding and withdrawals (9). A score of three or more on this scale indicates good quality. Second, both RCTs and nonrandomized controlled trials (non-RCTs) were assessed by an adequate description of allocation concealment, intention-to-treat (ITT) analysis, sample size calculation, description of withdrawals and use of appropriate statistical tests. Similarity between study group and control group was assessed on the basis of demographic data provided in the manuscript. All reports from each trial were utilized in assessing study quality. All corresponding authors were contacted by e-mail with a standardized letter detailing our assessment, requesting clarification of areas that were unclear from the publication and requesting a response to our quality assessment. First or senior authors were also contacted with the same letter if no reply was received from the corresponding author within 4 weeks. Supplementary information was returned for four studies and affected our initial assessment in one case where details of the randomization method were provided (10).

Data synthesis

The statistical package "R", *R Development Core Team*, was used to calculate summary effects for study outcomes. Meta-analysis was performed using the "metafor" package, *Wolfgang Viechtbauer*, available for "R". Heterogeneity was studied using the I^2 and Cochrane Q-tests for heterogeneity. In the absence of heterogeneity, studies were combined using a fixed effects analysis. Relative risk (RR) was used as a summary statistic for binary outcomes. Summary effects are given with 95% confidence intervals (95%CI). RRs from binary outcomes have been analyzed using the Pearson Chi^2 test unless $n < 10$, where Fisher's Exact test has been used. p value <0.05 has been used to indicate statistical significance. p value of <0.1 in the Cochran Q-test has been used to indicate significant levels of heterogeneity in meta-analysis.

Results

Initial literature searches identified 3649 references across all databases (Figure 1). Fifteen studies (10 RCTs and 5 non-RCTs) described in 28 references met the full inclusion criteria. Details of the included studies are shown in Table 1.

Methodological quality of the included studies was variable with included RCTs achieving between 0 and 3 points of 5 on the Jadad scale (Table 2). No studies described any form of blinding. Four studies described a randomization method that was consistent with allocation concealment (10–13), eight described a method that was not (14–21) and it was unclear in three studies (22–24). We could not say with any certainty that any of the studies performed an ITT analysis; descriptions of group switching postrandomization and pretransplantation were rarely provided. Withdrawals and dropouts were adequately accounted for in 10 studies (10,11,13–15,18,19,21,23,24). Only one study described a sample-size calculation (11). Appropriate statistical tests were described in 10 studies (10–14,17,19,20,23,24).

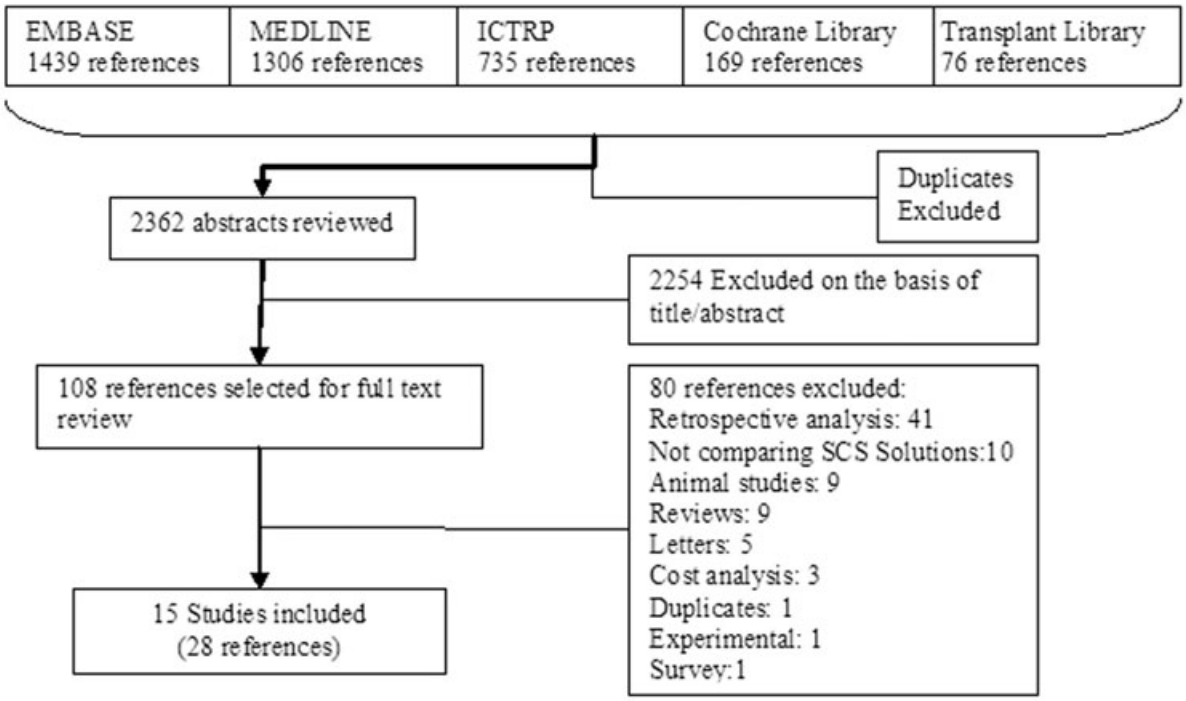

Figure 1: Flow chart of search strategy with inclusions and exclusions. ICTRP = International Clinical Trials Registry Platform; SCS = Static Cold Storage; Transplant Library = Library of RCTs from the Centre for Evidence in Transplantation.

Table 1: Details of included studies comparing two or more preservation solutions, grouped by solutions compared

Solutions compared	Study	Year	No. of patients	Study type	Donors	Country	Refs.
EC UW	Ploeg	1990	795 (343/352)	RCT	Not multiorgan	Multinational[1]	(11, 30–34)
	Hefty	1991	40 (20/20)	RCT	All	USA	(14, 35)
	Ishibashi	1994	90 (44/46)	RCT	DCD	Japan	(12)
EC HTK	Isemer	1988	18 (9/9)	Non-RCT	All	Germany	(15)
	Moisiuk	1996	108 (52/56)	Non-RCT	DCD	Russia	(16)
	Trushkov	2003	88 (54/34)	RCT	All	Latvia	(22)
	Groenewoud[2]	1990	569 (292/277)	RCT	DBD, not multiorgan	Eurotransplant[3]	(13, 36–40)
HTK UW	Groenewoud[2]	1990	611 (314/297)	RCT	DBD, not multiorgan	Eurotransplant[3]	
	Klaus	2007	51 (24/27)	RCT	All	Brazil	(18)
Celsior UW	Faenza	2001	187 (99/88)	RCT	All	Italy	(23)
	Pedotti	2004	441 (172/269)	RCT	Multiorgan	Italy	(17)
	Montalti	2005	50 (25/25)	RCT	>60 years old	Italy	(10)
HOC PBS	Lam	1989	184 (92/92)	Non-RCT	DBD	UK	(20, 41)
HOC Perfudex	Slapak	1979	47 (31/16)	Non-RCT	DCD	UK	(21)
UW UW Mod	Baatard	1993	82 (41/41)	RCT	All	France	(24)
IGL-1 UW	Badet	2005	223 (121/102)	Non-RCT	Multiorgan	France	(19, 42)

DBD = donor after brain death; DCD = donor after cardiac death = EC = Eurocollins; HOC = hyperosmolar citrate; HTK = histidine tryptophan ketoglutarate; IGL-1 = Institut Georges Lopez-1; PBS = phosphate buffered sucrose; UW = University of Wisconsin; UWMod = University of Wisconsin Modified.

[1]This multinational study included centers within the following countries: Austria, Belgium, France, Germany, The Netherlands, Luxembourg and Portugal.

[2]Parallel study of four interventional arms.

[3]The Eurotransplant International Foundation coordinates transplantation within the following countries: Austria, Belgium, Croatia, Germany, Luxembourg, The Netherlands and Slovenia.

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Table 2: Quality assessment of included studies

Study	Jadad score	Allocation concealment	Groups similar	Sample calculation	Withdrawals accounted for	Statistical tests described
Ploeg (30)	3	Yes	Yes	Yes	Yes	Yes
Hefty (14)	2	No	Yes	No	Yes	Yes
Ishibashi (12)	2	Yes	Yes	No	No	Yes
Isemer (15)	*	No	Unclear	No	Yes	None
Moisiuk (16)	*	No	Yes	No	No	Unclear
Trushkov (22)	1	Unclear	Unclear	No	No	Unclear
Groenewoud (13)	2	Yes	Yes	No	Yes	Yes
Klaus (18)	2	No	Yes	No	Yes	Unclear
Faenza (23)	2	Unclear	Yes	No	Yes	Yes
Pedotti (17)	1	No	Yes	No	No	Yes
Montalti (10)	3	Yes	Yes	No	Yes	Yes
Lam (20)	*	No	Yes	No	No	Yes
Slapak (21)	*	No	Yes	No	Yes	Unclear
Baatard (24)	2	Unclear	Yes	No	Yes	Yes
Badet (19)	*	No	Yes	No	Yes	Yes

*Nonrandomized controlled trials, not suitable for assessment using Jadad scale.

Delayed graft function

A wide range of overall rates of DGF were reported by the included studies (13–73%, Table 3). This may be partly explained by differences in the definitions used for DGF. The most common definition was a requirement for dialysis within the first week after transplantation, used by seven studies (10,12,14,17,19,20,23). Three studies defined DGF as at least two dialysis sessions within the first week (11,13,18) and one study defined it as at least three dialysis sessions within the first week (22). Two studies defined DGF by a lack of immediate urine production (15,16). Two studies did not report DGF as an outcome (21,24).

Eurocollins versus University of Wisconsin

Three RCTs compared UW with Eurocollins solution (EC) including a total of 825 kidneys (11,12,14). These trials had significant differences in their donor populations (1 study used DCD only; Ref. 12) and a large variation in the overall rate of DGF (range 15–73%). It was, therefore, inappropriate to combine the studies in a meta-analysis. Ploeg et al. conducted a large, good quality, multicenter RCT using a central randomization list to allocate groups (n = 695 kidneys; Ref. 11). They found that EC preserved kidneys had a significantly higher rate of DGF than UW preserved kidneys (RR = 1.46,95% CI 1.15–1.87, $p < 0.01$). Two smaller RCTs made the same comparison; Ishibashi et al. conducted a multicenter RCT (n = 90 kidneys) which found the risk of DGF to be equal with the two solutions (RR = 1.11,95% CI 0.87–1.43, p = 0.41; Ref. 12). There were a large number of unexplained withdrawals postallocation in this study. A central randomization table was used to allocate kidneys to preservation groups. Hefty et al. conducted a smaller, single-center RCT (n = 40 kidneys) finding no difference in the rate of DGF between the two groups (RR = 1,95% CI 0.23–4.37, p = 1; Ref. 14). The method of randomization was unclear.

Eurocollins versus Histidine-Tryptophan-Ketoglutarate

Two RCTs (13,22) and two non-RCTs (15,16) compared HTK with EC including a total of 783 kidneys. Significant differences between studies in terms of the donor populations (DCD only, Ref. 16); DBD only, Ref. 13), the overall rate of DGF (range 20–56%) and the definition of DGF prevented meta-analysis. Groenewoud et al. conducted the largest, multicenter RCT using kidney only donors (n = 569 kidneys; Ref. 13). DGF was defined as a requirement for two or more dialysis sessions in the first week postoperatively. The group found that the rate of DGF was significantly higher with EC than HTK stored kidneys (RR = 1.48,95% CI 1.18–1.85, $p < 0.01$). Trushkov et al. conducted a smaller, single-center RCT (n = 88 kidneys; Ref. 22). DGF was defined as a requirement for three or more dialysis sessions in the first week postoperatively. The rate of DGF was much higher with EC than HTK stored kidneys (RR = 23.55,95% CI 1.47–378.34, $p < 0.01$). It is unclear how many organs were eligible for this study and the group sizes differ considerably. In both RCTs, the method of randomization was unclear. Two non-RCTs defined DGF as a lack of immediate urine production. Moisiuk et al. (n = 108 kidneys) found the risk of DGF to be higher with EC than HTK stored kidneys (RR = 2.64,95% CI 1.46–4.77, $p < 0.01$; Ref. 16). Isemer et al. (n = 18 kidneys) found the risk of DGF to be equivalent with EC and HTK stored kidneys (RR = 1.5,95% CI 0.63–3.56, p = 0.64; Ref. 15). The method of allocation was unclear for both non-RCTs.

Celsior versus UW

Three multicenter RCTs compared UW with Celsior including a total of 678 kidneys (10,17,23). Pedotti et al. conducted the largest trial making this comparison (n = 441 kidneys) using a randomization list to allocate patients (17). The group found the risk of DGF to be equal for UW and Celsior-preserved kidneys (RR = 1.03,95% CI 0.72–1.46, p = 0.89). Faenza et al. conducted a large

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Table 3: Rate of delayed graft function (DGF) by solution studied and overall rates of DGF. Relative risk (RR) of DGF is Solution 1 versus Solution 2, >1 favors Solution 2. Studies grouped by comparisons made

Study	Patients with DGF/patients in study (%)	Mean cold ischemic time (h)	Solution 1 patients with DGF/patients in group (%)		Solution 2 patients with DGF/patients in group (%)		RR of DGF (95%CI)	p-Value[1]
Ploeg (11)	194/695 (28%)	24	EC	114/343 (33%)	UW	80/352 (23%)	1.46 (1.15 – 1.87)	<0.01
Hefty (14)	6/40 (15%)	23	EC	3/20 (15%)	UW	3/20 (15%)	1.00 (0.23 – 4.37)	1
Ishibashi (12)	66/90 (73%)	11	EC	34/44 (77%)	UW	32/46 (70%)	1.11 (0.87 – 1.43)	0.41
Isemer (15)	10/18 (56%)	NR	EC	6/9 (67%)	HTK	4/9 (44%)	1.50 (0.63 – 3.56)	0.64
Moisiuk (16)	38/108 (35%)	NR	EC	27/52 (52%)	HTK	11/56 (20%)	2.64 (1.46 – 4.77)	<0.01
Trushkov (22)	18/88 (20%)	NR	EC	18/54 (33%)	HTK	0/34 (0%)	23.55 (1.47 – 378.34)	<0.01
Groenewoud[2] (13)	204/569 (36%)	24	EC	119/277 (43%)	HTK	85/292 (29%)	1.48 (1.18 – 1.85)	<0.01
Groenewoud (13)	204/611 (33%)	24	UW	99/297 (33%)	HTK	105/314 (33%)	1.00 (0.8 – 1.25)	1
Klaus (18)	29/51 (57%)	20	UW	17/27 (63%)	HTK	12/24 (50%)	1.26 (0.77 – 2.06)	0.35
Faenza (23)	61/187 (33%)	17	Celsior	31/99 (31%)	UW	30/88 (34%)	0.92 (0.61 – 1.39)	0.69
Pedotti (17)	101/441 (23%)	15	Celsior	40/172 (23%)	UW	61/269 (23%)	1.03 (0.72 – 1.46)	0.89
Montalti (10)	25/50 (50%)	19	Celsior	12/25 (48%)	UW	13/25 (52%)	0.92 (0.53 – 1.61)	0.78
Lam (20)	39/160 (24%)	22	PBS	16/78 (21%)	HOC	23/82 (28%)	0.73 (0.42 – 1.28)	0.27
Badet (19)	29/223 (13%)	17	IGL-1	16/121 (13%)	UW	13/102 (13%)	1.04 (0.52 – 2.05)	0.92

EC = Eurocollins; HOC = hyperosmolar citrate; HTK = histidine tryptophan ketoglutarate; IGL-1 = Institut George Lopez-1; NR = not reported; PBS = phosphate buffered sucrose; UW = University of Wisconsin.

[1]Pearson Chi[2] test, Fisher Exact test if n<10.

[2]Parallel study of four interventional arms.

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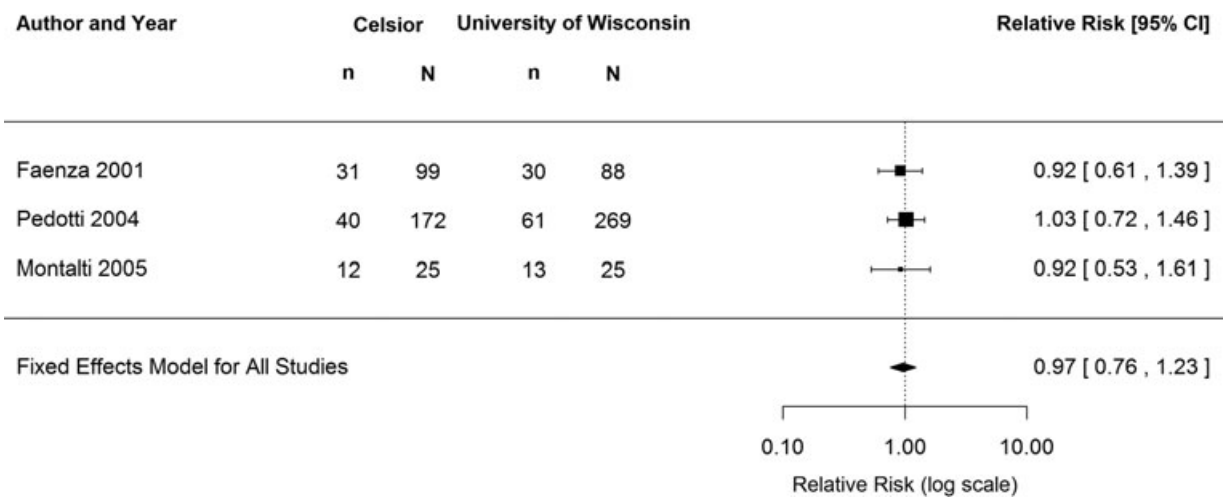

Figure 2: Forest plot to show the relative risk (RR) of delayed graft function (DGF) comparing Celsior with University of Wisconsin Solution. N = total patients in study arm, n = number of patients with DGF. Summary RR calculated by fixed effects meta-analysis, >1 favors UW. Squares represent individual study effects, diamond represents summary effect from meta-analysis. Horizontal bars represent 95% confidence intervals. I^2 test for heterogeneity = 0%, Cochran Q Test for heterogeneity Q = 0.19, p = 0.91.

trial (n = 187 kidneys) for which the method of randomization was unclear (23). The group found the risk of DGF to be equal for UW and Celsior-preserved kidneys (RR = 0.92,95% CI 0.61–1.39, p = 0.69). Montalti et al. conducted a smaller trial (n = 50 kidneys) using only donors over 60 years old (10). A computerized random number generator was used to allocate groups. This group also found the risk of DGF to be equal for UW and Celsior-preserved kidneys (RR = 0.92,95% CI 0.53–1.61, p = 0.78). All three studies defined DGF as a requirement for dialysis in the first week postoperatively. The overall risk of DGF in our meta-analysis of these studies was equal for both solutions (fixed effects meta-analysis, RR = 0.97,95% CI 0.76–1.23, p = 0.79, Figure 2). There was no heterogeneity, $I^2 = 0\%$, Cochrane Q-test for heterogeneity: Q = 0.19, p = 0.91.

HTK versus UW

Two RCTs compared UW with HTK including a total of 662 kidneys. Groenewoud et al. compared UW to HTK (n = 611 kidneys), parallel to their EC versus HTK study (described previously; Ref. 13). The group found the risk of DGF to be 33% for both HTK and UW-stored kidneys (RR = 1,95% CI 0.8–1.25, p = 1). Klaus et al. conducted a smaller, single-center RCT (n = 51 kidneys) defining DGF as a requirement for two or more dialysis sessions in the first week postoperatively (18). They found no difference in the risk of DGF (RR = 1.26,95% CI 0.77–2.06, p = 0.87). The method of randomization was unclear. As only two studies made this comparison, meta-analysis was not appropriate.

Other comparisons

Slapak et al. compared Perfudex with HOC in a non-RCT (n = 47 kidneys; Ref. 21). Kidneys stored in Perfudex on average required more dialysis sessions postoperatively than kidneys stored in HOC (4.4 vs. 1.7, p < 0.01). DGF as purely a requirement for dialysis was not presented. The method of allocation was unclear.

Lam et al. compared HOC with phosphate buffered sucrose (PBS) in a non-RCT (n = 104 kidneys; Ref. 20). Postoperative requirement for dialysis was not significantly different for HOC and PBS stored kidneys (RR = 0.73,95% CI 0.42–1.28, p = 0.35). Alternation was used to allocate kidneys to each group.

Two studies compared the original UW to two slight modifications of its composition, UW modified (UWMod) and Institut George Lopez-1 solution (IGL-1). Baatard et al. conducted a single-center RCT comparing UW with UWMod, which has hydroxyethyl starch, allopurinol and adenosine removed (n = 82 kidneys; Ref. 24). Results were provided for the average number of dialysis sessions postoperatively; there was no statistically significant difference between the groups (0.65 ± 5 sessions vs. 0.85 ± 5 sessions, p = NS). The method of randomization was unclear. Badet et al. compared UW to IGL-1 (which is UW with polyethylene glycol substituted for hydroxyethyl starch) in a non-RCT (n = 223 kidneys; Ref. 19). The risk of DGF was equivalent for IGL-1 and UW-stored kidneys (RR = 1.04,95% CI 0.52–2.05, p = 0.92). The method of allocation was unclear.

Donor quality and cold ischemic time

Subgroup analysis by quality of donor and length of cold ischemic time (CIT) was presented by four studies. Ploeg et al. compared DGF rates after <24 h CIT with 25–35 h and >35 h. Surprisingly, they did not find that the risk of DGF increased at longer CIT with either EC or UW preservation (11). This study also found that kidneys from

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Table 4: Graft survival rates. Studies grouped by solutions compared. Where numbers followed up were not stated in the papers the reported percentage graft survival is given. Blank spaces indicate no figures provided for that time-point in the original paper

Study	Group	1 month	3 months	12 months	24 months	36 months	48 months	60 months
Hefty (14)	UW	20/20 (100%)						
	EC	20/20 (100%)						
Ploeg (11)	UW		316/343 (92%)	265/300 (88%)				
	EC		295/335 (88%)[1]	233/282 (82%)[2]				
Ishibashi (12)	UW		96%	90%				
	EC		88%	84%				
Groenewoud[3] (13)	HTK			80%	76%	177/253 (70%)		
	EC			78%	71%	170/254 (67%)		
Moisiuk (16)	HTK			83%				
	EC			65%				
Trushkov (22)	HTK			88%				
	EC			79%				
Faenza (23)	UW				75%			
	Celsior				84%			
Pedotti (17)	UW	96%		91%				
	Celsior	96%		94%				
Montalti (10)	UW			96%				87%
	Celsior			92%				79%
Groenewoud (13)[3]	UW			81%	73%	191/281 (68%)		
	HTK			83%	77%	212/291 (73%)		
Klaus (18)	UW		26/27 (96%)	21/27 (78%)				
	HTK		23/24 (95%)	19/24 (79%)				
Lam (20)	PBS			85%			61/82 (74%)	
	HOC			85%			55/78 (71%)	
Badet (19)	UW			101/102 (99%)				
	IGL-1			118/121 (98%)				

EC = Eurocollins; HOC = hyperosmolar citrate; HTK = histidine tryptophan ketoglutarate; IGL-1 = Institut Georges Lopez-1; PBS = phosphate buffered sucrose.
[1]Log rank p = 0.09.
[2]Log rank p = 0.04.
[3]Parallel study of four interventional arms.

"bad" donors (n = 294, cardiac arrest, severe hypotension, serum creatinine >175 micromol/L, oliguria) did not have a significantly higher risk of DGF compared to "good" donors, regardless of the preservation solution used. Ishibashi et al. reported DGF rates for donors >60 years old as 100% for both EC and UW (12). Too few donors >60 years old were included for a statistical analysis (n = 10 in each study arm). Both Pedotti et al. and Faenza et al. found that longer CIT (>17 h and >18 h, respectively) did not distinguish between Celsior and UW, with both solutions being associated with an equal increase in the rate of DGF (17,23). Pedotti et al. also performed a subgroup analysis of donors >60 years old (n = 102), finding no difference between UW and Celsior. Montalti et al. only included donors >60 years old, finding that the risk of DGF was equally high with UW and Celsior (10).

Primary nonfunction

Five studies reported rates of PNF, although it was not defined by any study (11,16–19). Four studies had PNF rates under 5%, whereas one had PNF rates of 10% (16); this was a study of DCD only, in which 90% of the donors had cardiac arrest after head trauma. The average duration of cold ischemia was not reported by this study. Given these low-PNF rates, all included trials were underpowered to demonstrate a significant difference in this outcome between the preservation solutions examined.

Graft survival

Twelve studies reported graft survival rates at a variety of follow-up time-points (Table 4). Only one study reported log-rank p values for graft survival, Ploeg et al. (11). This study found there was an increased rate of graft loss for kidneys stored with EC compared to UW (82% vs. 88% survival at 12 months, log-rank p = 0.04). This finding was, in part, supported by the 12-month cumulative graft survival from the other RCT making the same comparison, 84% for EC and 90% for UW-stored kidneys (12). Unfortunately, there was insufficient data from this study to calculate the hazard ratio (HR). Overall, the reporting of numbers followed up at the declared time-points was poor, making HR calculation, and therefore meta-analysis, impossible. One study found an improved graft survival for Celsior-stored kidneys compared to UW-stored kidneys (23), whereas the other two studies making this comparison found no statistically significant difference (10,17). Three studies reported graft survival for comparisons of HTK with EC (13,16,22) and two compared HTK with UW (13,18), finding no

Table 5: Episodes of acute rejection at declared follow-up time-points. Information regarding immune suppression is given where available from the original paper

						Immune suppression	
Study	Follow-up	Solution	Episodes	Patients	Episodes per patient	Induction	Maintenance
Isemer	Unclear	EC	10	9	1.11		
		HTK	4	9	0.44		
Baatard	3 months	UW	7	41	0.17	ATG	CsA+Aza+Pred
		UW Mod	6	41	0.15		
Ishibashi	3 months	UW	21	46	0.46	+/-ATG	CsA/Tac+MMF/Aza
		EC	25	44	0.57		
Pedotti	1 month	UW	59	269	0.22	ATG/OKT/ Basiliximab	CsA/Tac+MMF +Pred
		Celsior	31	172	0.18		
Montalti	Predischarge	UW	2	25	0.08		CsA/Tac
		Celsior	2	25	0.08		
Badet	Unclear	UW	13	102	0.13		CsA/Tac/Rap+ Pred+ MMF/FTY740
		IGL-1	15	121	0.12		
Klaus	12 months	UW	10	27	0.38		
		HTK	8	24	0.33		
			Patients with acute rejection				
Faenza	Predischarge	UW			13%		CsA/Tac
		Celsior			12%		

ATG = antithymocyte globulin; Aza = Azathioprine; CsA = Cyclosporine; MMF = mycophenolate mofetil; OKT = Muromonab; Pred = prednisolone; Rap = Rapamycin; Tac = Tacrolimus.

significant difference in graft survival. Equal graft survival was also reported for comparisons of HOC with PBS (20) and UW with IGL-1 (19).

The two largest studies, which examined EC, HTK and UW, compared long-term graft survival for kidneys with and without DGF, demonstrating that DGF was associated with worse long-term graft survival for kidneys preserved with any one of these solutions (11,13).

Renal function

Graft function postoperatively was reported at a variety of time-points and in different units. One study comparing EC to UW found a more rapid fall in serum creatinine within the first week with UW (11), although at 3–4 months follow up there was no significant difference, and this was supported by the other two studies making this comparison (12,14). One study comparing EC with HTK reported faster normalization of serum creatinine and lower levels up to 2 weeks postoperatively with HTK-stored kidneys (22). Another study making the same comparison found a faster normalization of serum creatinine with HTK-stored kidneys as well, though from a limited subset of its included patients (13). Levels remained lower until 30 days after surgery. Two smaller studies found the time to normalization of serum creatinine was equal for both HTK and EC (15,16). All three studies comparing UW to Celsior found no significant difference in postoperative serum creatinine before discharge (10,23) or up to 2 weeks follow up (17). One study reported comparable serum creatinine for kidneys stored in UW and HTK from 1 month up to 1 year postoperatively (18). The other study making this comparison also found no significant difference in levels up to 1 month in a subset of its patients (13).

Patients receiving UW and UWMod-stored kidneys were found to have similar serum creatinine from 1 month up to 1 year postoperatively (24). IGL-1 stored kidneys were associated with lower serum creatinine than UW-stored kidneys from day 6 to 12 months postoperatively (19). Patients receiving HOC-stored kidneys had significantly lower serum creatinine than those receiving Perfudex-stored kidneys at day 10 postoperatively (21).

Acute rejection

Eight studies reported rates of acute rejection (10,12,15,17–19,23,24; Table 5). Acute rejection was only defined as proven on biopsy by one study, Klaus et al. (18). This group found that acute rejection episodes during the first 12 months were equal for UW and HTK-stored kidneys (0.38 and 0.33 episodes per patient, $p = 0.78$). Acute rejection was not defined in the remainder of the studies. The preservation solution was not related to acute rejection in any study that reported this as an outcome. One study reported the percentage of patients experiencing rejection (23), the others declared total episodes of rejection (i.e. some patients in these studies had multiple episodes). Graft loss of 3.3% due to hyper-acute rejection was reported by one study (13), and graft loss due to acute rejection was reported by three studies (10,11,16). Numbers of graft losses due to acute rejection were very small (range 1.9–4%) and no study reported that the

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Table 6: Patient survival rates at declared follow-up time-points

Study	Preservation solutions	Postoperative	1 month	3 months	12 months
Ploeg	EC			96%	94%
	UW			98%	95%
Pedotti	Celsior		100%		99%
	UW		100%		98%
Badet	IGL-1				98%
	UW				100%
Montalti	Celsior	100%			
	UW	100%			
Klaus	HTK				86%
	UW				84%

EC = Eurcollins; HTK = histidine tryptophan ketoglutarate; IGL-1 = Institut Georges Lopez-1.

preservation solution was related to graft loss from acute rejection.

Patient survival

Limited data was available for long-term patient survival; it was only reported in five studies (10,11,17–19; Table 6). The choice of preservation solution was not related to worse patient survival in any of these studies. Limited information on numbers followed up prevented us from performing a statistical analysis.

Discussion

This systematic review has examined the evidence for the commonly used static cold preservation solutions in renal transplantation. We have found that the risk of DGF is influenced by the choice of preservation solution for static cold storage. However, the evidence assessed here cannot provide a specific RR for DGF when using one preservation solution over another. The risk of DGF is increased with EC-stored kidneys when compared to both UW and HTK in the largest, best quality RCTs. This is congruent with the findings of the smaller studies that made the same comparisons and registry data (1). On the basis of the three RCTs that compared UW with Celsior and two that compared UW with HTK, we conclude that these three solutions are associated with a comparable risk of DGF and this is partly supported by analysis of registry data (3). Previous systematic reviews have included an analysis of studies comparing UW with Celsior (5) and UW with HTK (6), concluding as we did that the risk of DGF was equivalent.

Long-term graft survival was worse for EC than UW-stored kidneys in the one good quality RCT that provided follow-up data for this comparison. Absolute graft survival was also worse for EC than HTK-stored kidneys in the three studies with long-term follow-up. However, not enough information was provided to aggregate the data. The association between renal grafts suffering DGF and worse long-term graft survival has been described previously (4).

Analysis of the Collaborative Transplant Study (CTS) suggests UW-stored kidneys with up to 24 h of CIT have a lower rate of graft loss than EC-stored kidneys, and equivalent rate of graft loss compared to HTK and HOC-stored kidneys. With CIT beyond 24 h, the risk of graft loss increases more with EC-, HTK- and HOC-stored kidneys than it does with UW-stored kidneys (1). Interestingly, the two RCTs comparing HTK to UW had mean CIT of 23 and 20 h (13,18); CTS data analysis suggests that no difference in graft loss would be seen at this length of CIT. At odds with the CTS analysis, United Network for Organ Sharing (UNOS) data shows that HTK storage for long CIT is not associated with increased graft loss when compared to UW (3). Overall, however, UNOS data suggests that HTK is associated with an increased risk of graft loss compared to UW from 1 year posttransplant, regardless of CIT.

Data regarding the secondary outcomes (PNF, acute rejection, patient survival and posttransplant renal function) was insufficient in the included studies to draw strong conclusions. Given the overall low rates of acute rejection, PNF and patient death, much larger studies would be required to reveal any differences. There is a suggestion that posttransplant serum creatinine may fall more quickly with UW or HTK than EC-stored kidneys, though the exact clinical significance of this is unclear. Similarly, IGL-1 storage seemed to result in improved serum creatinine compared to UW storage even at 12 months postoperatively in one study; again exactly what effect this would have is unclear.

A unique finding of this systematic review is the lack of RCTs comparing HOC for renal preservation to any of the solutions in use before its development, or to newer solutions such as UW and HTK. Despite this, it was used for the preservation of large numbers of kidneys on a background of animal experiments (25,26) and trials involving machine perfusion (27). Moreover, it is still used for the static cold storage of 2–3% of kidneys included in CTS.

Overall, the methodological quality of the included studies was poor. Randomization was not universally used and the method of allocation to groups was not often concealed, allowing clinicians to predict which kidneys would be allocated to each study group. Participants were excluded from analysis postallocation in many studies and the reporting of numbers followed up was lacking. Blinding of participants

or investigators was not declared in any study, though this is to some extent mitigated by the measurement of objective outcomes such as graft loss. Furthermore, this study has highlighted the need to establish a universal definition for DGF that is both validated and objective. Given that the decision to dialyse is subjective, a lack of allocation concealment can lead to the introduction of bias through the manipulation of this outcome.

In the present review, we have concentrated on randomized and prospective comparative studies to present the best quality evidence. There is also a large body of evidence available from retrospective studies and registries. We deliberately excluded retrospective studies to avoid the biases inherent in registry data, such as selection bias and performance bias. Although RCTs are not without bias, these can be mitigated when the body of evidence is substantial. We found the volume of clinical trial evidence to be small and, given the various comparisons made, the amount of data had to be further divided. Despite this, the outcomes reported by the studies included here are largely in agreement with the available registry data. This study was conducted in accordance with the preferred reporting items in systematic reviews and meta-analysis (PRISMA) statement but did not achieve all recommended reporting items (28); the review protocol could not be prospectively registered and published, as the study was too far advanced to be accepted by the UK National Institute for Health Research's Prospective Register of Ongoing Systematic Reviews (NIHR-PROSPERO) when this system became available in February 2011 (29). The assessment of reporting bias could also not be completed as the small number of studies making each comparison precluded funnel plots.

There is no difference in the incidence of DGF with the use of Celsior, HTK and UW. A preference for one solution over another could theoretically be based upon the relative cost of each solution, in combination with the recommended flush volume. However, these three solutions do not vary greatly in price; Celsior costs US$250 per liter, HTK costs US$195 per liter and UW costs US$190 per liter. These differences in price are small when contrasted with the much cheaper HOC, which costs approximately US$15 per liter. Even with the small difference in recommended aortic flush volumes (Celsior 3–5 liters; HTK 5–6 liters and UW 2-4 liters), there does not seem to be support for the use of one of these three solutions over another on the basis of cost. Intra-aortic flush volumes and back-table flush volumes may have affected outcomes in the included studies via an increased rate of graft cooling with larger volumes; however this information was not adequately reported in the included studies. Another consideration is the efficacy of each solution in the preservation of nonrenal organs perfused *in situ* at the same time as the kidneys. We are planning future work to examine the evidence for preservation methods in nonrenal abdominal organs.

The choice of preservation solution has an effect upon short-term outcomes for renal allografts, which may in turn affect long-term outcomes. From the limited evidence identified, Celsior, HTK and UW are associated with a comparable risk of DGF and graft loss.

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Disclosure

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