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REVIEW ARTICLE

A systematic review and meta-analysis of cold *in situ* perfusion and preservation for pancreas transplantation

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Abstract

Background: This study aimed to identify the most effective solution for *in situ* perfusion/preservation of the pancreas in donation after brain death donors, in addition to optimal *in situ* flush volume(s) and route(s) during pancreas procurement.

Methods: Embase, Medline and Cochrane databases were utilized (1980–2017). Articles comparing graft outcomes between two or more different perfusion/preservation fluids (University of Wisconsin (UW), histidine–tryptophan–ketoglutarate (HTK) and/or Celsior) were compared using random effects models where appropriate.

Results: Thirteen articles were included (939 transplants). Confidence in available evidence was low. A higher serum peak lipase (standardized mean difference 0.47, 95% CI 0.23–0.71, $I^2 = 0$) was observed in pancreatic grafts perfused/preserved with HTK compared to UW, but there were no differences in one-month pancreas allograft survivals or early thrombotic graft loss rates. Similarly, there were no significant differences in the rates of graft pancreatitis, thrombosis and graft survival between UW and Celsior solutions, and between aortic-only and dual aorto-portal perfusion.

Conclusion: UW cold perfusion may reduce peak serum lipase, but no quality evidence suggested UW cold perfusion improves graft survival and reduces thrombosis rates. Further research is needed to establish longer-term graft outcomes, the comparative efficacy of Celsior, and ideal perfusion volumes.

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Introduction

Hypothermia has long been the dominant paradigm in organ preservation, and is most effectively initiated by the cold vascular *in situ* flush.[1–3] Subsequently, organs are retrieved and immersed in the same preservation fluid as is used for the flush for cold static storage (CS) and transportation prior to transplantation.

Multiple types of perfusion/preservation fluids have been investigated in abdominal organ procurement, with various combinations and volumes of perfusion.[2–6] However, there is no universal consensus regarding the optimal perfusion/preservation fluid, nor the route(s) or ideal volume of flush. There are considerable variations in recommendations in different jurisdictions.[1,7,8] UK guidelines recommend 50–70 ml/kg of UW solution for aortic perfusion in the retrieval of the pancreas from donation after brain death (DBD) donors, with or without UW portal perfusion *in situ* or on the back-table, and no pre-flush.[7] Australian recommendations in DBD donors suggest the use of either low-viscosity solution alone, such as HTK, or low-viscosity pre-flush followed by 1.5–2 L of UW flush; centers are given leniency with regards to aortic-only or dual perfusion.[8] There are no clear guidelines from the American Society of Transplant Surgeons regarding DBD organ procurement. Eurotransplant advocates for HTK or UW aortic only perfusion, without a pre-flush; the option of portal perfusion is provided if the pancreas is not procured.[1]

Clinical evidence regarding perfusion/preservation fluids is not unequivocally in favor of one solution over another for pancreas preservation, although a single registry analysis suggests a higher incidence of graft loss with HTK compared to UW solution for preservation of the pancreas.[9,10]

The relative efficacy of the various preservation solutions for the pancreas, in the context of *in situ* perfusion volume and route, has not been systematically explored. Therefore, the aims of this systematic review and meta-analysis were to synthesize the existing evidence regarding effective solution for *in situ* perfusion and subsequent CS of the DBD pancreas, and to identify the optimal *in situ* flush volume(s) and route(s) during pancreas procurement.

Methods

The protocol for this systematic review was prospectively registered with PROSPERO (registration number – CRD42016038993).[11] The review was undertaken with adherence to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[12]

Study selection and eligibility

Randomized controlled trials (RCT; or quasi-RCTs) and/or observational articles were deemed eligible for this review, without language restriction. An article was only included if it presented data for a minimum of at least 10 patients/transplants per study group, and included information regarding perfusion fluid route(s), flush volume(s), back-table perfusion and final preservation of the pancreas. Pediatric studies, animal experiments, articles without a control group, and studies exploring machine perfusion, were excluded from the analysis. Conference abstracts were also excluded due to insufficient perfusion data and/or quality. Only data from DBD donors was included; if mixed DCD and DBD donor data was presented in an article, this study was excluded from further analysis if the DBD patient data could not be extracted.

Literature search strategy

Literature searching was conducted by two independent researchers, and encompassed the Embase, Medline and Cochrane databases, and the Cochrane Register of Controlled Trials (1980 to January 2017). The full search strategy is outlined in Supplemental Digital Content (SDC) 1 (Table). A manual search of relevant full-text article reference lists was conducted to identify further potential eligible articles.

Data extraction

Two independent reviewers extracted study data into a predetermined template for the following parameters:

Baseline characteristics and study demographics

Author(s), study date and period, center(s); donor patients/transplants, type of pancreas transplant; donor cardiac arrest and vasopressor/inotrope requirements, donor and recipient age, donor intensive care unit (ICU) stay, donor body mass index (BMI); aortic or dual perfusion (flush), use of pre-flush and type (a pre-flush is defined as the removal of static blood from organs using a solution that is different to the final flush and preservation solution), use of back-table perfusion and its type and route, perfusion volume(s), perfusion (preservation) solution(s) used, procurement technique; cold ischemic time (CIT) and warm ischemic time (WIT).

Recipient outcomes

Primary study outcomes included peak amylase and lipase in the first week post-transplantation, the number of pancreatitis episodes, and thrombotic graft loss. Other secondary outcomes of interest included C-peptide and HbA1C at last follow-up, acute rejection rates, graft survival (one, six & 12-month – survivals beyond this reported only sporadically), hospital length-of-stay (LOS), and surgical complications (e.g. exocrine pancreatic leak). Graft pancreatitis was variably defined in the included studies. The study definition was accepted in this analysis. The definitions included a serum amylase levels >2.5 times the upper limit of normal (ULN) from post-operative day two onwards,[13] surgical appearance on reperfusion,[14] amylase levels >2.5 times the ULN with associated pain,[15] pancreatic enzyme derangement with increased insulin requirements,[16] or amylase >2 times ULN with associated clinical or radiologic features of pancreatitis.[17–19]

Data analysis

Median ischemic times, donor/recipient ages, perfusion volumes, and graft survival were calculated (to allow a comparison between Celsior and UW or HTK) based on the number of patients in each study group. If necessary prior to meta-analysis, continuous variables initially underwent standardized mean difference (SMD) calculations between study groups using the Practical Meta-analysis Effect Size Calculator.[20]

Meta-analyses were conducted using studies with directly comparable groups, as determined by the nature of perfusion solution used, perfusion route(s), and graft ischemic times. Only observational studies were included in meta-analyses as there were insufficient RCTs with comparable groups eligible for meta-analysis. Risk ratios (RR) and SMD between two comparable groups were estimated using Dersimonian Laird random effects models. Publication bias was assessed using funnel plots. Heterogeneity was evaluated using the I^2 statistic, and considered the I^2 thresholds of <25%, 25–49%, 50–75% and >75% to represent low, moderate, high and very high heterogeneity. Subgroup analyses/meta-regression to further define sources of heterogeneity could not be conducted due to insufficient data. Meta-analyses were conducted, where applicable, using Comprehensive Meta-Analysis Version 2.2 (Biostat, Inc., Englewood, New Jersey, USA).

Risk of bias

The Cochrane Collaboration's bias assessment tool was utilized to formally assess RCTs, and includes the domains of random sequence generation, allocation concealment, blinding, incomplete outcome data and selective reporting.[21] Cohort studies undergoing meta-analysis were screened for bias through the utilization of the Newcastle–Ottawa scale; this incorporates in its assessment of bias the domains of representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, comparability of cohorts, assessment of outcomes and follow-up timing and attrition.[22] Publication bias was determined by examining funnel plots for each meta-analysis parameter analyzed.

Quality of evidence

The overall quality of evidence and thus confidence that may be derived from the summary estimates derived from meta-analyses was assessed utilizing the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) guidelines.[23]

Results

Overall study selection and categories

Articles comparing different perfusion/preservation solutions and techniques for pancreas transplantation were analyzed. The study selection process is summarized in Fig. 1. A total of 805

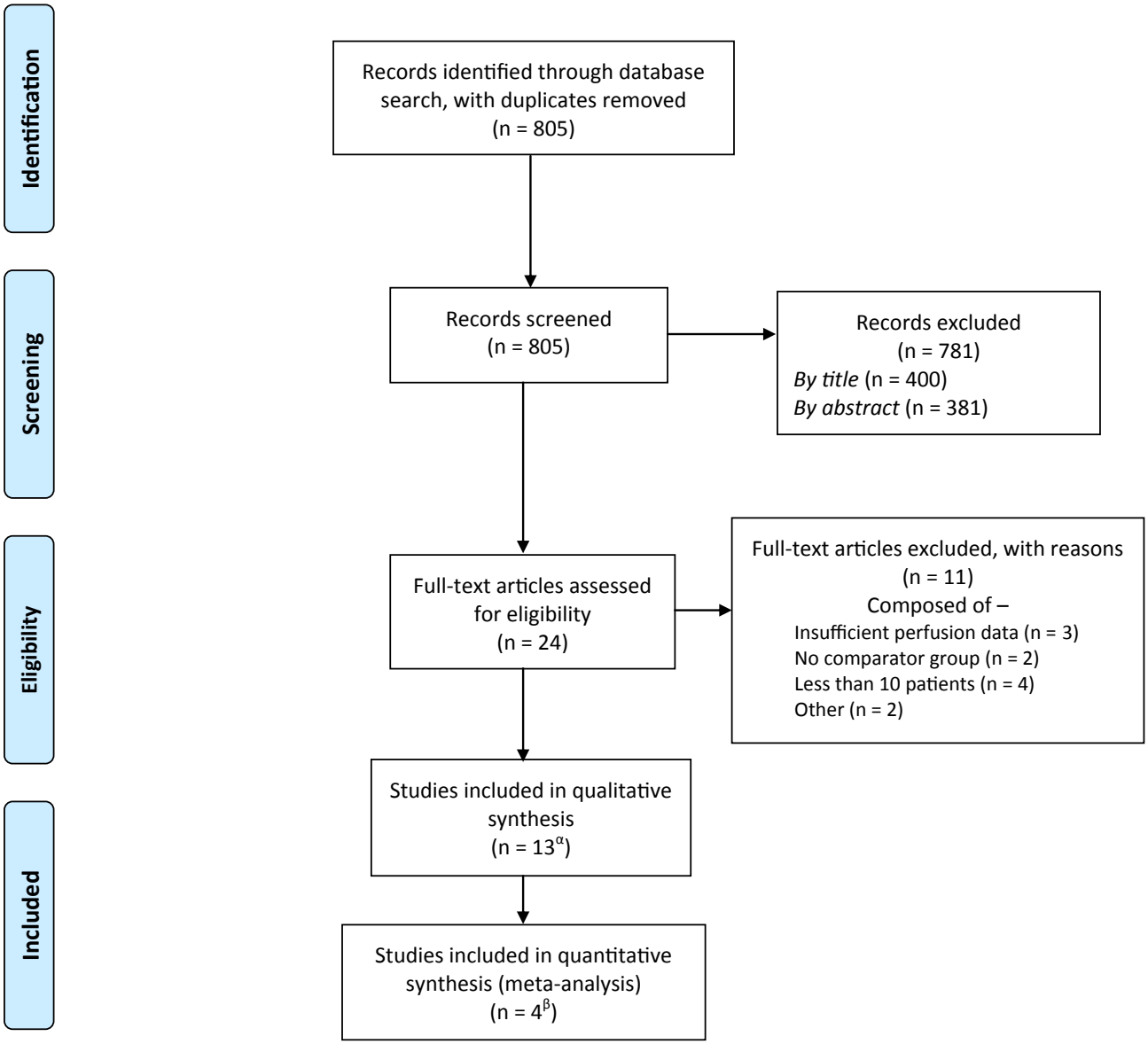


Figure 1 Study selection flow diagram. α Includes articles with overlapping results that were analyzed together. β Parameters analyzed: peak amylase & lipase, graft pancreatitis, thrombotic graft loss, hospital length of stay, and one-month graft survival

Table 1 Baseline characteristics of the included studies

Pancreas studies	Study type	Study year	Organs retrieved[f]	Total transplants	Comparator/intervention groups	*n* per group
Alonso *et al*.[15]	Cohort	2008	NR	97	UW perfusion & CS	81
					HTK perfusion & CS	16
Becker *et al*.[24]	Cohort	2007	NR	95	UW perfusion & CS	47
					HTK perfusion & CS	48
Boggi *et al*.[17,18]	RCT	2004	Liver (*en bloc*)	112	UW perfusion & CS	56
					Celsior perfusion & CS	56
Englesbe *et al*.[25]	Cohort	2006	NR	77	UW perfusion & CS	41
					HTK perfusion & CS	36
Fridell *et al*.; Agarwal *et al*.[26–28]	Cohort	2010	Liver (*en bloc*)	308	UW perfusion & CS	50
					HTK perfusion & CS	258
Gonzalez *et al*.[13]	Cohort	2005	Liver (*en bloc*)	46	UW perfusion & CS	30
					EC **pre-flush** + UW perfusion & CS	16
Manrique *et al*.[19]	Cohort	2006	NR	72	UW perfusion & CS	44
					Celsior perfusion & CS	28
Nicoluzzi *et al*.[29]	RCT	2008	NR	31	UW perfusion & CS	15
					Celsior perfusion & CS	16
Potdar *et al*.[14]	Cohort	2004	NR	33	UW perfusion & CS	17
					HTK perfusion & CS	16
Schneeberger *et al*.[16]	RCT	2009	NR	68	UW perfusion & CS	41
					HTK perfusion & CS	27
Summary data	R – 7 studies RCT – 3 studies	Range – 1995–2009	Liver (*en bloc*) – 3 studies	Total – 939	NA	939

CIT, cold ischemic time; CS, cold storage; EC, Euro-Collins; HTK, histidine-tryptophan-ketoglutarate; NA, not applicable; NR, not recorded; P, prospective; PAK, pancreas after kidney transplant; PTA, pancreas transplant alone; R, retrospective; RCT, randomized control trial; SPK, simultaneous pancreas kidney transplant; UW, University of Wisconsin; WIT, warm ischemic time.

[a] Total ischemic time.

[b] Statistically significant difference between the two study groups (i.e. $p < 0.05$).

[c] Dual perfusion indicates aortic + portal perfusion; in the Fridell *et al*. data-set,[26–28,31] the portal circulation was slowly perfused with plasmalyte, and was accessed through the inferior mesenteric vein.

[d] One liter EC pre-flush + 1 L formal UW flush.

[e] Not recorded by perfusion fluid; for Manrique *et al*.,[19] in total there were 67 SPKs and 5 PAKs, whilst for Schneeberger *et al*.,[16] there were 65 SPKs, 2 PTAs, and 1 PAK.

[f] In addition to the pancreas.

records were identified. Following screening, 10 data-sets (incorporating 13 studies with overlapping data) were included in qualitative analyses, out of which only four cohort studies had sufficient data and were eligible for meta-analyses.[13–19,24–29] Seven study data-sets were observational in nature, and three were RCTs.

Risk of bias assessment

The overall risk of bias for observational studies was considered high. A summary of bias assessment using the Newcastle–Ottawa scale is provided in SDC 2 (Table). All studies provided a representative cohort of pancreas donors and recipients, and a clear description of the exposure/intervention chosen. Comparability of study cohorts, as determined by similar donor/recipient ages and/or ischemic times, was demonstrated in 62.5% of cohort studies included in meta-analyses. A majority of studies failed to specify whether the pancreas was retrieved *en bloc* with the liver, and whether a rapid retrieval technique was utilized.

The overall risk of bias for RCTs was largely indeterminate due to the difficulty to assess a majority of domains (Table, SDC 3). Risk of bias with respect to random sequence generation and blinding was difficult to ascertain/unclear in two of the three studies (Table, SDC 3). All studies had a low risk of bias with respect to incomplete outcome data. Both allocation concealment and selective reporting could not be assessed from available data in any of the included RCTs.

n, SPK/PTA/PAK	Donor age (mean)	Recipient age (mean)	CIT (hrs) (mean)	Aortic or dual perfusion	Total perfusion (flush) volume (l)
52/5/24	26.0	42.3	15.4	Aortic	2.6
12/1/3	27.3	41.7	13.9	Aortic	4.9
47/0/0	34.6[b]	43.3	12.0	Aortic	4.8
48/0/0	29.7[b]	39.5	10.1	Aortic	9.7
NR	29.3	39.3	10.1	Aortic	5.6
NR	31.0	38.7	10.8	Aortic	7.9
24/3/14	24.6	37.8	7.7	Aortic	3
22/1/13	25.2	37.5	9.5	Aortic	5
11/22/17	27.2	41.9	9.3[a]	Dual[c]	3.3
160/39/57	26.2	42.8	8.3[a]	Dual[c]	3.9
30/0/0	NR	35.4	13.5	Aortic	2
16/0/0	NR	35.4	13.7	Aortic	2[d]
NR[e]	27.1	36.2[b]	8.3	Dual	2.4
NR[e]	25.3	41.0[b]	8.7	Dual	2.4
15/0/0	30	33	15	Aortic	0.8
15/0/0	28	33	16	Aortic	0.8
10/4/3	29.5[b]	36.9	15.1	Aortic	3.5
6/6/4	21.9[b]	41.3	14.0	Aortic	9
NR[e]	NR	44.2	11.8	Aortic	3
NR[e]	NR	43.0	10.8	Aortic	6.5
SPK – 664 PTA – 90 PAK – 144	Median – 26.2 Range – 21.9–34.6	Median – 41.9 Range – 33.0–44.2	Median – 10.1 Range – 7.7–16.0	NA	NA

Funnel plots were generated to assess publication bias, but were uninformative owing to only three or four studies being included in each comparison (Graph, SDC 4).

Overall quality of study evidence is summarized utilizing the GRADE evidence profile (Table, SDC 5). Quality of evidence is either low or very low for all outcome measures investigated. Overall study evidence was downgraded due to the observational nature of studies included in meta-analyses, and small sample sizes and/or wide confidence intervals (imprecision).

Baseline characteristics of included studies

Whole pancreas perfusion study characteristics, including comparator groups, donor and recipient ages and ischemic times, are summarized in Table 1. Six whole pancreas studies compared UW to HTK perfusion; eight of the studies overall specified the utilization of aortic-only pancreas perfusion. A total of 939 pancreatic transplants were included in the analysis; these comprised, where specified, 664 simultaneous pancreas-kidney transplants, 90 pancreas transplants alone, and 144 pancreas-after-kidney transplants. Median CIT was 10.1 h, and median donor and recipient ages were 26.2 and 41.9 years, respectively. A rapid procurement technique was utilized in four articles[30]; retrieval type was not clearly specified in the other studies. All studies investigated *in situ* perfusion with subsequent CS in DBD donors.

Pancreas retrieval was performed *en bloc* with the liver, with separation of the organs on the back-table, in three of the

included study series. The remaining studies did not specify what organ(s) were procured in addition to the pancreas, or the order in which they were removed.

Perfusion and preservation characteristics

Table 1 outlines the perfusion and preservation fluids utilized in each study group, in addition to the routes and volumes of *in situ* perfusion. A 'pre-flush' to remove static blood was only utilized in one included article.[13] Aortic-only perfusion was most prevalent in the pancreas studies, with UW being the most popular perfusion solution and was used at lower volumes than HTK (3 L [range 0.88–5.6 L] compared to 6.5 L [range 4.9–9.7 L], respectively). Back-table perfusion with UW was used in two studies (1 L, volume only recorded in one study),[14,28] and HTK in two studies (1 L, volume only recorded in one study).[14,28] This back-table flush was given via the splenic artery and superior mesenteric artery (SMA)/coeliac axis. Two studies explicitly specified not using back-table flush.[17,29] In one of two pancreas back-table flush studies,[14] only *in situ* aortic perfusion was performed, whilst dual perfusion was utilized in the other article due to combined liver-pancreas procurement.[28,31]

Transplant outcomes

Peak serum amylase/lipase and graft pancreatitis rates

Of the seven studies that included peak serum amylase and/or lipase as outcomes, only four (57.1%) provided sufficient data for meta-analyses. Pancreatic allografts being perfused with and subsequently preserved in UW had a lower serum peak lipase compared to those preserved in HTK solution (SMD 0.42, 95% CI 0.14–0.69; p = 0.003; I^2 = 0; n = 205 patients; Fig. 2). However, the difference in peak amylase did not reach statistical significance (SMD 0.32, 95% CI −0.13 to 0.76; p = 0.159; I^2 = 67.0; n = 302 patients; Fig. 2).

In pancreatic allografts perfused and subsequently preserved in UW compared to HTK, via the aortic-only route, graft pancreatitis rates were considerably higher in the HTK group in Alonso *et al.*'s study (9 of 16 [56.3%] HTK patients versus 19 of 81 [23.5%] UW patients; p = 0.01).[15] There was no statistical difference in pancreatitis rates between UW and HTK in the study by Potdar *et al.*, as defined by pancreatic appearance upon reperfusion (5 of 16 [31.3%] HTK patients compared to 4 of 17 [23.5%] UW patients; p = 0.62).[14]

Of the three UW versus Celsior studies, including two studies with aortic-only perfusion and one study utilizing dual perfusion, there were no significant differences in peak amylase, lipase or graft pancreatitis rates.[17–19,29]

Thrombotic graft loss rates

Of the eight studies that reported thrombotic graft loss rates, only three (37.5%) provided sufficient data for meta-analyses. There were no significant differences between thrombotic graft loss rates between pancreata perfused via the aorta using UW or HTK (time period not recorded in most studies; n = 269 patients; Fig. 2).

Thrombotic graft loss rates were also no different in the articles comparing UW and Celsior *in situ* pancreas perfusion and preservation.[17–19,29]

Hospital length-of-stay

Hospital length-of-stay (LOS) was reported in three articles, all of which compared UW and HTK, and were also eligible for meta-analysis. Mean difference between hospital LOS in the HTK and UW groups was 2.91 days (95% CI −0.04 to 5.87; p = 0.053; I^2 = 0; n = 174 patients; Fig. 2).

Exocrine pancreatic leak and fistula formation

Pancreatic leakage, as evidenced by a peri-pancreatic fluid collection, abscess and/or fistula formation, was not uniformly or consistently reported and hence could not be statistically analyzed. The leak rate for UW *in situ* perfusion/preservation groups was reported in six studies, with a median of 10.0% (range 0–13.3%). Median leak rates were similar in both HTK and Celsior perfusion/preservation groups, at 11.1% (range 11.1–31.3%, n = 2 studies) and 10.0% (10.1–17.9%, n = 3 studies), respectively.

Graft survival

One-month graft survival was reported in five studies, out of which four (80%) were eligible for meta-analysis. There was no significant difference in one-month pancreatic graft survivals subsequent to UW or HTK *in situ* aortic perfusion and preservation, although there was a trend favoring UW (n = 302 patients; Fig. 2). Twelve-month graft survival data for this comparator group was available for only two studies,[15,25] and as such formal meta-analyses were not conducted. In the study by Alonso *et al.*, pancreatic graft survival at 12 months after UW and HTK perfusion/preservation was 90% and 81%, respectively (p = 0.09); corresponding levels in Englesbe *et al.*'s article were 89% and 72.5%, respectively (p > 0.05).[15,25]

To allow for survival comparisons between Celsior perfusion/preservation and UW or HTK, one, six, and 12-month pancreas graft survivals were collated. Survival data is presented in Table 2. Survival data for pancreas procurement after dual perfusion was only available from one study[28] and thus no meaningful comparisons could be made. More data were available for the assessment of aortic-only perfusion; aortic perfusion using UW provided a median 12-month graft survival of 90%, compared to 81% for HTK-perfused grafts. Only one Celsior aortic-only perfusion article was available (from a single center in Pisa, Italy), with 12-month pancreas allograft survival of 95.9%.[18]

Other perfusion/preservation group comparisons

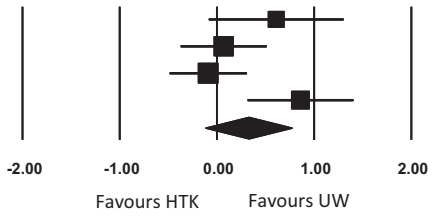
Fridell *et al.* compared UW and HTK dual perfusion and preservation; there were no significant differences in peak amylase or

a

Study name	Outcome	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Potdar et al., 2004	Peak amylase	0.610	0.356	0.127	-0.088	1.308	1.712	0.087
Englesbe et al., 2006	Peak amylase	0.070	0.228	0.052	-0.378	0.518	0.306	0.759
Becker et al., 2007	Peak amylase	-0.090	0.205	0.042	-0.492	0.312	-0.438	0.661
Alonso et al., 2008	Peak amylase	0.860	0.280	0.079	0.310	1.410	3.066	0.002
		0.319	0.226	0.051	-0.125	0.763	1.410	0.159

n = 302 patients

$I^2 = 67.0$



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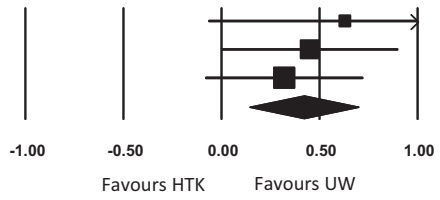
Study name	Outcome	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Potdar et al., 2004	Peak lipase	0.630	0.357	0.127	-0.069	1.329	1.765	0.077
Englesbe et al., 2006	Peak lipase	0.450	0.231	0.053	-0.003	0.903	1.946	0.052
Becker et al., 2007	Peak lipase	0.320	0.207	0.043	-0.085	0.725	1.550	0.121
		0.417	0.141	0.020	0.140	0.694	2.951	0.003

n = 205 patients

$I^2 = 0$



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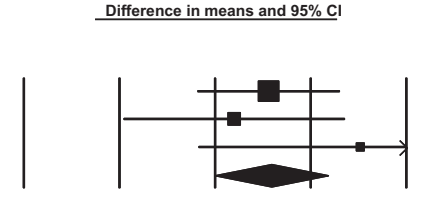
Study name	Outcome	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Englesbe et al., 2006a	Hospital LOS	2.800	1.914	3.663	-0.951	6.551	1.463	0.143
Englesbe et al., 2006b	Hospital LOS	1.000	2.967	8.803	-4.815	6.815	0.337	0.736
Alonso et al., 2008	Hospital LOS	7.600	4.333	18.773	-0.892	16.092	1.754	0.079
		2.916	1.508	2.273	-0.039	5.872	1.934	0.053

n = 174 patients

$I^2 = 0$



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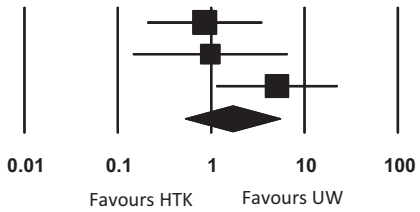
Study name	Outcome	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value
Englesbe et al., 2006	Thrombotic graft loss	0.854	0.205	3.564	-0.216	0.829
Becker et al., 2007	Thrombotic graft loss	0.979	0.144	6.667	-0.022	0.983
Alonso et al., 2008	Thrombotic graft loss	5.063	1.121	22.866	2.108	0.035
		1.673	0.518	5.400	0.860	0.390

n = 269 patients

$I^2 = 37.9$



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Study name	Outcome	MH risk ratio	Lower limit	Upper limit	Z-Value	p-Value
Potdar et al., 2004	1-month graft survival	3.176	0.139	72.747	0.723	0.469
Englesbe et al., 2006	1-month graft survival	1.898	0.487	7.392	0.924	0.356
Alonso et al., 2008	1-month graft survival	2.500	0.500	12.510	1.115	0.265
Becker et al., 2007	1-month graft survival	0.979	0.340	2.820	-0.039	0.969
		1.515	0.737	3.117	1.130	0.259

n = 302 patients

$I^2 = 0$

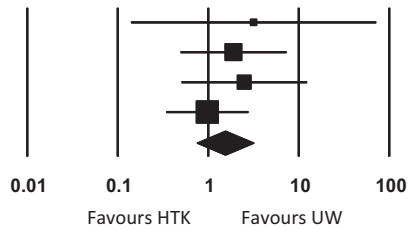

Figure 2 Forest plots for (a) peak amylase, (b) peak lipase, (c) hospital length-of-stay, (d) thrombotic graft loss rates, and (e) one-month graft survival after *in situ* aortic perfusion and preservation of the pancreas with UW or HTK

Table 2 Comparison of median one, six and twelve-month graft survivals in pancreatic grafts obtained after UW, HTK or Celsior perfusion. Data presented as median (range).[b]

Pancreas	UW (aortic perfusion)	UW (dual perfusion)	HTK (aortic perfusion)	HTK (dual perfusion)	Celsior (aortic perfusion)	Celsior (dual perfusion)
1-month survival, % (range; n studies)	95 (87.0–100; 5)	94 (NA[a]; 1)	87.5 (85–93.8; 4)	95 (NA; 1)	NA	NA
6-month survival, % (range; n studies)	90 (80.0–95.8; 6)	NA	85.4 (81–86.1; 4)	NA	95.9 (67–95.9; 2)	NA
12-month survival, % (range; n studies)	90 (82.6–95.8; 4)	86 (NA; 1)	81 (72.5–85.4; 3)	92 (NA; 1)	95.9 (NA; 1)	NA

HTK, histidine–tryptophan–ketoglutarate; NA, not applicable; UW, University of Wisconsin.
[a] NA here indicates that there was no extractable study data available.
[b] Median overall survivals weighted by total patient numbers in each study group.

lipase, whilst pancreatitis and thrombotic graft loss rates were not recorded.[28] The one study that employed an Euro-Collins pre-flush followed by a formal UW flush found no differences with the UW-only perfusion/storage group in terms of graft pancreatitis and thrombotic graft loss rates.[13]

Discussion and conclusions

This systematic review has compared the various different DBD pancreas perfusion and preservation conditions, and analyzed their potential for impacting graft outcomes in the recipient. Overall the quality of evidence was poor, with wide confidence intervals for effect estimates and only a small number of studies. Furthermore, the majority of included data was from younger donors, with relatively short CITs. At best, UW *in situ* perfusion and preservation results in less biochemical pancreatic enzyme release in comparison to HTK, and may manifest in lower graft pancreatitis rates, although definitions for this vary between studies. There were no clear differences between UW and HTK for other short-term graft parameters, including thrombotic graft loss. HTK-preserved pancreata tended to have lower graft survivals in comparison to UW. Despite meta-analyses not being possible in the comparison between UW and Celsior, there was no evidence of deleterious consequences in the short and longer term when Celsior was utilized. Study heterogeneity and limited data precluded any conclusions being drawn regarding ideal perfusion volumes or routes, although aortic-only perfusion with lower volumes of UW was the most common occurrence.

An important consideration in the interpretation of data from this study is the separate but also likely synergistic impact on the pancreatic allograft of *in situ* perfusion during procurement, and also subsequent CS preservation in the same perfusion fluid. As such, it is very difficult to tease out the individual effects of the initial flush and then subsequent preservation on graft outcomes. This suggests that both factors must be considered before analyzing the efficacy of a CS preservation fluid, and as such, only articles including both procurement and preservation data were included in this study.

A number of abdominal organ perfusion fluids exist, which vary in constituents/composition and viscosities. The three most commonly employed solutions for the pancreas, which also tend to be the same for all abdominal organ procurement, are UW, HTK and Celsior. These all contain impermeants designed to counteract cellular edema, buffers to counteract ischemic acidosis, and energy substrates to encourage ATP formation upon reperfusion.[32] UW differs further in that it is an 'intracellular' type solution that is of higher viscosity due to the presence of hydroxyethyl starch and as such its flow rates during organ flushing are lower.[32,33] In contrast, higher flush volumes are recommended in particular for HTK to allow for equilibration of the fluid's electrolyte content with the graft extracellular space, although this has been challenged by others.[14,28,34,35]

UW compared to HTK pancreas perfusion and preservation resulted in a reduction of recipient peak lipase, which may translate to lower graft pancreatitis rates. A formal comparison of graft pancreatitis was precluded not only by insufficient studies reporting this parameter, but more importantly by the significant variability in how graft pancreatitis was defined.[36] Clinical acute graft pancreatitis must be distinguished from histologic pancreatitis and definitions incorporating clinical signs, biochemical parameters and/or imaging findings should be preferred over the utilization of individual parameters.[36,37] If indeed UW is superior to HTK with respect to recipient graft pancreatitis, this may at least partially be related to the 'low-flow' nature of the pancreas being better-suited to the more viscous UW solution compared to faster flush rates achieved with HTK and the potential for hyper-perfusion.[38]

The impact of perfusion/preservation fluid on graft outcomes may also be modified by the duration of cold ischemia. In the study by Englesbe *et al.*, where both study groups had a CIT of less than 10 h, UW was not clearly advantageous in comparison to HTK.[25] In contrast, CITs of more than 12 h were seen in Alonso *et al.*'s article, with superior outcomes in the UW group, possibly suggesting that UW is a better preservative in the event of longer ischemic times.[15] Although pancreas articles could not be meta-analyzed for differences between UW and Celsior, this comparison was made in three different studies, including two

studies with CITs of 12 h or less, and showed no significant outcome disparities between either perfusion solution.[17–19,29] Overall, especially when attempts are made to minimize pancreas CIT, it is possible that the choice of preservation solution may not significantly impact subsequent transplantation outcomes.

Another important consideration is the quality of the donor pancreas, as determined by factors such as donor age. Median donor age for all included studies in this systematic review was 26.2 years. Current evidence indicates a decline in pancreas transplantation rates, in part related to donor factors, and therefore the future may see the increased utilization of so-called expanded criteria donors, including DCD and older DBD donors.[39–41] There is conflicting evidence regarding post-transplantation outcomes when older and/or DCD pancreata are utilized, however.[41–44] Although one strategy in the expanded criteria donor cohort could include the minimization of CITs through local allocation alone, optimal and novel donor management and preservation strategies will likely need to be employed to further enhance recipient outcomes.[39,40,43,45]

Pancreas retrieval is almost always undertaken in a multi-organ retrieval setting, where the liver and kidneys are also often procured. As such, high quality perfusion and preservation of the pancreatic allograft needs to be undertaken without compromising the quality and outcomes of other retrieved organs, in particular the liver. Only three of the studies included here specified liver procurement in addition to the pancreas, but hepatic allograft outcomes were not discussed.[13,18,28] A systematic review and meta-analysis by O'Callaghan *et al.* however did not show any significant differences in liver transplantation outcomes when UW, Celsior or HTK solutions were utilized.[6] In contrast, a recent European registry analysis suggested a higher risk of liver allograft loss when HTK solution was employed, which was in fact also shown in a pancreas registry analysis.[9,46] A further confounding factor not considered by these studies is the effect of the route of *in situ* perfusion, namely aortic-only in comparison to dual perfusion. Few comments can be made regarding pancreas retrieval after dual perfusion from this present article, due to the lack of included studies investigating this technique. Nevertheless, pancreatic procurement after dual perfusion is discouraged due to possible risks of increased graft injury stemming from venous congestion and graft edema.[2,47] Significantly, dual *in situ* perfusion does not seem to provide clear benefits for liver transplantation outcomes, and as such its routine use must be questioned, especially in a multi-organ retrieval setting.[48,49] We are currently in the process of formally investigating dual compared to aortic-only *in situ* perfusion for liver retrieval in a further systematic review.

Procurement teams have the option of employing a 'pre-flush' prior to the final *in situ* organ flush. A pre-flush is advocated by relatively few authors as a means to improve final preservation fluid distribution within the organ, especially prior to the use of UW flush due to its high viscosity and its possible tendency to aggregate with red blood cells.[33] Pre-flush employment may also decrease the total volume of UW required, thereby reducing preservation costs due to the significantly greater expense of UW in comparison to fluids such as HTK.[13,27] Gonzalez *et al.*'s study was the only article included here that utilized a pre-flush.[13] These authors compared Euro-Collins pre-flush followed by UW aortic flush with UW aortic flush alone for pancreas procurement, and showed no significant post-transplantation outcome differences between both over a three-month time period.[13] It is clear that most major retrieval units do not utilize or report on a pre-flush technique, however, and if it continues to be utilized by some units it would be worth a larger prospective trial to ensure its value and ensure it is not in fact detrimental.

Certain biases and disadvantages must be considered in the interpretation of findings from this review. Firm conclusions could not be made regarding longer-term graft outcomes and ideal perfusion routes and volumes, owing to a paucity of available data. Furthermore, the fact that most included articles were retrospective in nature introduced confounding and heterogeneity to the cumulative data; this was reflected by low or very low quality of evidence as determined by the GRADE assessment. Despite our attempts to minimize biases and account for study heterogeneity by only meta-analyzing comparable study cohorts, and using a random effects model in all cases, the cumulative evidence presented here must be interpreted with caution.

In summary, this is the first review to systematically investigate DBD donor pancreas *in situ* perfusion and preservation prior to transplantation. Although cumulative evidence suggests that UW may reduce ischemia-reperfusion injury of the pancreas, as manifested by a lower peak lipase, longer-term outcomes, the comparative efficacy of UW and Celsior, and ideal perfusion volumes remain uncertain. The development of uniform pancreas procurement and preservation guidelines will require additional studies that are prospective in nature and higher-powered, although this may be difficult owing to declining pancreas transplantation activity in some centers. Currently, it can only be concluded that pancreas procurement after *in situ* aortic perfusion and subsequent cold static storage using UW solution remains safe and is the most commonly reported option.

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Previous communication

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Author contributions

AH – research design, data collection and analysis, writing of paper, revision of paper.
GW – data analysis, writing of paper, revision of paper.
JL – data analysis, writing of paper, revision of paper.
VL – data analysis, revision of paper.
HP – research design, data analysis, writing of paper, revision of paper.
WH – research design, data collection and analysis, writing of paper, revision of paper.
All authors have approved the final article.

Conflicts of interest

None declared.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.hpb.2017.07.012.