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REVIEW

Preservation solutions used during abdominal transplantation: Current status and outcomes

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Abstract

Organ preservation remains an important contributing factor to graft and patient outcomes. During donor organ procurement and transportation, cellular injury is mitigated through the use of preservation solutions in conjunction with hypothermia. Various preservation solutions and protocols exist with widespread variability among transplant centers. In this review of abdominal organ preservation solutions, evolution of transplantation and graft preservation are discussed followed by classification of preservation solutions according to the composition of electrolytes, impermeants, buffers, antioxidants, and energy precursors. Lastly, pertinent clinical studies in the setting of hepatic, renal, pancreas, and intestinal transplantation are reviewed for patient and graft survival as well as financial considerations. In liver transplants there may be some benefit with the use of histidine-tryptophan-ketoglutarate (HTK) over University of Wisconsin solution in terms of biliary complications and potential cost savings. Renal grafts may experience increased initial graft dysfunction with the use of Euro-Collins thereby dissuading its use in support of HTK which can lead to substantial cost savings. University of Wisconsin solution and Celsior are favored in pancreas transplants given the concern for pancreatitis and graft thrombosis associated with HTK. No difference was observed with preservation solutions with respect to graft and patient survival in liver, renal, and pancreas transplants. Studies involving intestinal transplants are sparse but University of Wisconsin solution infused intraluminally in combination with an

intra-vascular washout is a reasonable option until further evidence can be generated. Available literature can be used to ameliorate extensive variation across centers while potentially minimizing graft dysfunction and improving associated costs.

Key words: Graft preservation; Kidney; Liver; Pancreas; Intestine

Core tip: Preservation of abdominal organs during transplant remains an important factor in patient and graft survival. Considerable variation exists between institutions with respect to the preservation solution of choice with an uncertain impact on patient and graft survival. Herein, pertinent clinical studies were reviewed to highlight the best available evidence in the selection of preservation solutions for abdominal transplantation. Histidine-tryptophan-ketoglutarate (HTK) may improve the incidence of biliary complications in hepatic transplants while minimizing costs for renal transplants. However, the use of HTK is dissuaded in pancreas transplants in favor of University of Wisconsin and Celsior solutions given the potential for graft thrombosis with HTK.

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INTRODUCTION

The demand for donor organs for transplantation far exceeds the supply, however recipients fortunate enough to receive suitable donor organ may encounter morbidity and potential graft loss secondary to preservation and transportation of those organs. The implications are immense as delayed graft function and potential graft failure confer substantial risks of morbidity and mortality, in addition to considerable financial expenditure and further depletion of an already scarce resource for those requiring re-transplantation.

EVOLUTION OF TRANSPLANTATION AND DONOR ORGAN PRESERVATION

Initial attempts at renal transplantation remained hindered by inadequate organ preservation and graft rejection until 1954 when Joseph Murray performed the first successful renal transplant in monozygotic twins[1]. Prior attempts at renal transplantation consisted of graft placement in the thigh using femoral vascular anastomosis and a skin ureterostomy however, graft failure ultimately ensued within 5 mo of transplant[1]. Intra-abdominal placement of renal grafts was later favored to minimize infectious risks[1]. Transplants between non-monozygotic individuals continued to have poor outcomes initially as adequate immunosuppression had not been properly addressed. Hume *et al*[2] reported a series of 9 patients with renal homotrasplants (7 cadaveric and 2 living donors) where all individuals ultimately required explantation by 180 d. Improved outcomes involving cadaveric renal grafts occurred with the introduction of new immunosuppression agents in the 1960s[3]. Calne *et al*[3] had patient survival rates up to 2.5 years (in 3 of 20 renal transplants) with the use of azathioprine in addition to steroids and the use of *ex-vivo* hypothermic graft cooling to 4 ℃ with lactate ringers (containing albumin and heparin).

Following early clinical success with renal transplantation, transplantation of other abdominal organs was attempted. The first successful pancreas transplant was described by Kelly *et al*[4] who performed a combined kidney-pancreas transplant in a 28-year-old diabetic. The first liver transplant with a survival rate > 1 mo was described in by Starzl *et al*[5] in 1967. Seven patients were described in this initial series, 6 of whom underwent organ preservation with hypothermia (2 ℃), hyperbaric oxygen, and a intra-hepatic flush of diluted blood (containing heparin, dextran, and procaine) through the superior mesenteric vein of the graft[5]. In the remaining case, cardiopulmonary bypass was instituted after death to achieve cooling and perfusion[5].

Initial efforts to improve graft and patient survival focused on improved operative technique, immunosuppresion, and organ preservation[6]. Pioneering efforts at organ preservation necessitated a strategy to reduce the use of intracellular substrates and accumulation of harmful toxins during ischemia[7]. This goal was achieved through total body cooling of donors (living or deceased) or surface cooling of grafts alone[6]. Hypothermic conditions to 15 ℃ reduced tissue oxygen consumption to 12% of normal and in turn minimized tissue damage[6]. However, canine kidneys subjected to hypothermia at 2 ℃-4 ℃ for 24 h had partial evidence of ischemic damage and were non-functional[6]. Damaging effects of hypothermia included mitochondrial dysfunction, ion channel disruption, perturbation of Ca^{2+} homeostasis, ATP reduction, accumulation of xanthine oxidase and reactive oxygen species which can be detrimental to cellular viability[8]. Therefore, hypothermia alone was insufficient for adequate organ preservation as cellular metabolism persisted leading to organ deterioration albeit, at a slower rate than without institution of any cooling measures[9]. As such, preservation solutions were incorporated into mainstream graft preservation techniques (cold static storage and pulsatile perfusion) for cytoprotection against ongoing cellular insults and still remain a fundamental method of current graft preservation.

A myriad of preservation solutions exist with different compositions of impermeants, buffers, antioxidants, and energy substrates aimed at maximizing graft survival and function[10]. Early preservation solutions consisted of diluted blood and lactate ringers solution until the development of Collins and Belzer solutions[3,11,12]. Collins attempted to recapitulate intracellular ionic conditions and reduce hypothermia induced graft edema through a combination of mannitol, phenoxybenzamine, procaine, glucose, KH_2PO_4, K_2HPO_4, KCL, $NaHCO_3$, and $MgSO_4$[11]. The alpha-blocker phenoxybenzamine stabilized lysomal membranes[11]. However, phenoxybenzamine and heparin were found to be non-essential components while procaine had nephotoxicity as the drug was converted to p-aminobenzoic[13]. Furthermore, there was a concern for magnesium phosphate crystal precipitation and ample protection could be provided without magnesium[14]. As such, heparin, procaine, phenoxybenzamine, and magnesium were removed to form a modified Collins solution known as Euro-Collins (EC) after agreement by the Eurotransplant Committee in 1976[14]. Conversely, Belzer solution consisted of type specific plasma with KCl, mannitol, decadron, $MgSO_4$, and insulin[12]. An early comparison involving 686 kidneys grafts stored in Collins solution (146 grafts) compared to Bezler solution revealed the use of Collins preservation solution was associated with improved 1 year graft survival (71% Collins *vs* 50% Belzar) and 1 year patient survival (58% Collins and Belzer 48%) suggesting the composition of different preservation solutions indeed play an important role in overall outcome[15].

After widespread acceptance of EC as the preservation solution of choice for 2 decades, its superiority was challenged with the introduction of newer solutions in the late 1980s[16]. In 1988, first successful experiences with University of Wisconsin (UW) solution for liver transplant was described in a series of 17 patients and adequate protection was provided for ischemic times greater than 8 h[17]. UW's efficacy was later shown for 11 combined renal-pancreas and 4 isolated pancreas transplants for up to 19 h without an occurrence of graft pancreatitis, thrombosis, or primary graft non-function[18]. However, the high molecular weight components within UW such as hydroethyl starch resulted in a highly viscous solution that was implicated in graft dysfunction[19]. As such, UW's popularity and utilization was decreased by less viscous solutions such as Celsior (CEL) and Histidine-tryptophan-ketoglutarate (HTK) that allow for high flow rates under gravity conditions alone while reducing the requirement for graft flushing prior to reperfusion[16,20]. HTK's first clinical use was described in 1989 in 14 patients receiving liver grafts[16]. CEL was first used in cardiac graft protection in 1998 and successful adoption in liver, renal, and pancreas preservation followed shortly afterwards[21-25].

Cold storage preservation of grafts during the *ex-vivo* timeframe remains an important determinant of graft and patient survival. While important, optimal preservation solutions for use in machine perfusion are outside the context of this review and have been described elsewhere[26]. A standardized approach to cold storage of organs is lacking and there is considerable clinical protocol variation among transplant centers[27]. Investigation into the ideal preservation strategy for abdominal transplantation is useful in helping to facilitate evidence-based decisions among clinicians and diminish variability.

RESEARCH

Studies pertaining to preservation of intra-abdominal organs were obtained using pubmed. Searches were conducted using 1 term from each of the following two groups (to yield combinatory search strategies): (1) "University of Wisconsin", "Euro-collins", "Celsior", "HTK"; and (2) "liver", "kidney", "pancreas", "intestine". Additional pertinent studies were obtained from investigation of references within relevant articles. Articles were limited predominantly to clinically based manuscripts (where appropriate) that were accessible.

CLASSIFICATION OF PRESERVATION SOLUTIONS

Preservation solutions differ in composition yet share similar objectives of reducing graft edema, intracellular acidosis, production of reactive active oxygen species, and providing energy substrates for metabolism (Table 1).

Intracellular vs extracellular solutions

Each solution may be classified according to its similarity to the intracellular or extracellular milieu. Early preservation strategies such as EC and UW solutions aimed at recapitulating an intracellular environment with high potassium/low sodium concentrations[27,28]. High potassium solutions minimize energy expenditure, intracellular potassium egress, and blunt cellular edema of grafts that result from hypothermia induced Na^+/K^+ membrane protein dysfunction[7,29,30]. However, high potassium solutions carry the potential for vasospasm and endothelial dysfunction[31]. Standard EC solution (Na^+ 10 and K^+ 115 mmol/L) substituted with high sodium/low potassium concentrations (Na^+ 115 and K^+ 10 mmol/L) result in better oxygenation and lower vascular resistance compared to standard EC[30]. As a result, newer strategies favored the creation of extracellular (low potassium/high sodium) based solutions such as HTK and CEL[7]. Likely, intracellular and extracellular solutions are equivocal with both strategies being effective[32,33].

Impermeants: The absence of substrate delivery during ischemia and hypothermia induced Na^+/K^+ protein pump dysfunction lead to sodium and water retention within grafts[7]. Graft edema results in diminished tolerance to anoxia[34]. The ability to counteract this effect had been suggested as the most important

Table 1 Comparison of select preservation solutions

	Euro-Collins	University of Wisconsin	Histidine-tryptophan-ketoglutarate	Celsior
Intracellular/extracellular	Intracellular	Intracellular	Extracellular	Extracellular
Sodium	10	25	15	100
Potassium	115	120	10	15
Impermeant	Glucose Mannitol	Lactobionate Raffinose Hydroxyethyl starch	Mannitol	Lactobionate Mannitol
Buffer	Phosphate Bicarbonate	Phosphate	Histidine	Histidine
Antioxidant	Mannitol	Allopurinol glutathione	Tryptophan Mannitol Histidine	Glutathione Mannitol Histidine
Energy precursor	---	Adenosine	Glutamic acid/glutamate	Glutamic acid/ glutamate
Others		Insulin Dexamethasone	Ketoglutarate	

All units expressed in mmol/L.

property of preservation solutions[7]. EC utilizes glucose as an impermeant to combat cellular edema however, this is suboptimal as glucose will eventually penetrate into cells thereby, negating its osmotic properties[34]. Mannitol is an additional component of EC that is also present within HTK and used to mitigate the effects of hypothermia induced edema[35]. Contrarily, UW consists of lactobionate, raffinose and hydroxyethyl starch as measures against graft edema with lactobionate appearing to be the most effective countermeasure[7,17]. CEL uses a hybrid approach to that of HTK and UW with mannitol and lactobionate[35].

Antioxidants: Reperfusion injury results from the generation of oxygen free radicals through enzymes such as xanthine oxidase and can lead to lipid peroxidation of cellular membranes and cell death[36]. Antioxidants are useful to alleviate cellular stress and damage resulting from free radical formation therefore, incorporation into preservation solutions has been favorable[35]. UW contains the xanthine oxidase inhibitor allopurinol and the reducing agent glutathione[7,33]. CEL also contains glutathione however, it has a greater reducing capacity than UW as most of the glutathione in UW is present in the oxidized state[37]. Notably, CEL also contains the free radical scavengers mannitol and histidine while EC contains mannitol alone[35]. Tryptophan, mannitol and histidine ascribe antioxidant properties to HTK[35].

Buffers: Metabolic acidosis during graft ischemia results from anaerobic metabolism and ATP hydrolysis which can lead to cellular dysfunction[38]. Proton accumulation can be alleviated by the action of buffers, which maintain physiologic intracellular pH and promote normal cellular activity[38,39]. EC has phosphate and bicarbonate buffering systems while UW is reliant upon phosphate alone[38]. Histidine is a non-essential amino acid present in HTK and CEL which lends a relatively high buffering capacity compared to UW and EC[38,40,41].

Energy precursors: The presence of energy precursors leads to higher levels of adenosine 5'triphosphate (ATP) generation after ischemia and improved mitochondrial function[35]. UW contains adenosine while HTK and CEL contain glutamic acid/glutamate as energy precursors[35,41]. Greater levels of ATP and improved mitochondrial function are found in CEL and UW cultured cells relative to HTK[35]. UW contains many additional components such as penicillin, insulin, and dexamethasone however, these likely play minor roles in overall graft preservation[7].

LIVER PRESERVATION

The liver is more sensitive to ischemia than renal or pancreas grafts. Pokorny *et al*[42] were able to double the cold ischemia time to a median of 9.6 h with the use of HTK, while Erhard *et al*[43] observed viable grafts with cold ischemia time of up to 15 h using UW or HTK.

A multi-center European trial involving 214 patients showed HTK to be safe and efficacious for use in liver transplantation with a 1 year graft survival of 80%, 1 year patient survival of 83%, and a primary graft non-function rate of 2.3%[42]. As such, there has been much interest in comparing HTK to UW (Table 2). A prospective study between UW and HTK found no difference in 1, 6, and 12 mo graft survival (UW 91.7%, 86.2%, 81.7% *vs* HTK 92.0%, 85.5%, 80.8%, respectively; *P* not stated) or patient survival (UW 93.1%, 87.7%, 84.6% *vs* HTK 93.1%, 86.2%, 82.1%, respectively; *P* not stated)[44]. There was a difference in liver function tests at post-operative day 1 that had normalized within 7 d[44]. However, this effect did not have any clinical implications. A randomized controlled trial involving 60 patients stratified to receive either HTK or UW supported these findings with equivocal patient survival (UW 74%, HTK 77%, $P = 0.347$) and initial graft survival (UW 80%, HTK 87%, $P = 0.213$)[43]. Many other studies have found no significant differences between UW and HTK with respect to graft and patient

Table 2 Selected clinical studies involving liver preservation solutions

Ref.	Solution	Cases	Patient survival	Graft survival
UW *vs* HTK				
Erhard *et al*[43]	UW *vs* HTK	60 (UW 30, HTK 30)	No diff (30 mo) (UW 74%, HTK 77%)	No diff (3 mo) (UW 80%, HTK 87%)
Mangus *et al*[44]	UW *vs* HTK	378 (UW 204, HTK 174)	No diff (1 yr) (UW 84.6%, HTK 82.1%)	No diff (1 yr) (UW 81.7%, HTK 80.8%)
Rayya *et al*[45]	UW *vs* HTK	137 (UW 68, HTK 69)	No diff (1 yr) (UW 78%, HTK 78%)	No diff (1 yr) (UW 78%, HTK 71%)
Mangus *et al*[51]	UW *vs* HTK	698 (UW 327, HTK 371)	No diff (1 yr) (UW 88%, HTK 87%)	No diff (1 yr) (UW 84%, HTK 86%)
Avolio *et al*[46]	UW *vs* HTK	39 (UW 22, HTK 17)	No diff (not stated) (UW 82%, HTK 88%)	No diff (6 mo) (UW 80.9%, HTK 85.7%)
Canelo *et al*[47]	UW *vs* HTK	134 (UW 71, HTK 63)	No diff	No diff
Celsior *vs* (HTK or UW)				
Nardo *et al*[57]	CEL *vs* HTK	40 (CEL 20, HTK 20)	No diff (1 yr) (CEL 90%, HTK 85%)	No diff (1 yr) (CEL 90%, HTK 75%)
García-Gil *et al*[56]	CEL *vs* UW	80 (CEL 40, UW 40)	No diff (1 yr) (CEL 85.7%, UW 79.8%)	No diff (1 yr) (CEL 78%, UW 75.5%)
Cavallari *et al*[55]	CEL *vs* UW	173 (CEL 83, UW 90)	No diff (1 yr) (CEL 87%, UW 89%)	No diff (1 yr) (CEL 85%, UW 83%)
Lopez-Andujar *et al*[53]	CEL *vs* UW	196 (CEL 92, UW 104)	No diff (1 yr) (CEL 83%, UW 83%)	No diff (1 yr) (CEL 81%, UW 80%)
Pedotti *et al*[54]	CEL *vs* UW	175 (CEL 79, UW 96)	No diff (1 yr) (CEL 89.9%, UW 90.6%)	No diff (1 yr) (CEL 83.3%, UW 85.4%)

Diff: Difference; UW: University of Wisconsin; CEL: Celsior; HTK: Histidine-tryptophan-ketoglutarate.

survival[45-47]. One of the largest studies to address this issue was carried out by Feng *et al*[48] who performed a meta-analysis involving a combined total of 1200 patients with no notable differences between the two solutions[48]. The utility of UW to HTK has also been studied in extended criteria donors[49,50]. Mangus *et al*[51] found no statistical difference in 1 year graft (RR = 1.01; 95%CI: 0.92-1.11; *P* = 0.86) or patient survival (RR = 1.01; 95%CI: 0.92-1.10; *P* = 0.87) in extended criteria donors with the use of UW or HTK.

There have been many studies favoring HTK over UW strictly based on cost. Costs of HTK are roughly 33% to 50% less compared to the corresponding volume of UW[49,50]. Early use of HTK suggested 10-20 L of solution was necessary for liver transplants however, it was later shown that liver grafts could be safely protected using less than 4L of HTK[44]. The volume of HTK used by Chan *et al*[49] and Testa *et al*[50] was approximately 1.5 fold higher than UW; despite this discrepancy, the overall costs still favored a modest financial advantage associated with the use of HTK. Mangus *et al*[44] identified a $422 (USD) savings per patient with the use of HTK over UW which is similar to the suggested estimates of Ringe *et al*[52]. Over the course of a year, one high volume institution had estimated cost savings of $67520 by switching from UW to HTK[44].

CEL has been investigated in multiple studies as a viable alternative solution for use in liver transplantation. In a prospective study by Lopez-Andujar *et al*[53] containing 196 patients (UW 104 and CEL 92), one year graft survival rates (UW 80% *vs* CEL 81%, *P* not stated) and one year patient survival (UW 83% *vs* CEL 83%, *P* not stated) were not statistically different, which is congruous with the findings of Pedotti *et al*[54]. Two randomized studies have been carried out to investigate the effect of UW to CEL in greater detail. Similar to a study by Cavallari *et al*[55], García-Gil *et al*[56] found no difference in graft survival at 1 year (UW 75.5% *vs* CEL78%, *P* not stated) or patient survival at 1 year (UW 88% *vs* CEL 85.7%, *P* not stated. Given the non-inferiority of CEL in these studies, investigations have been carried out to compare CEL to other popular solutions such as HTK, and it was again found to be comparable[57].

Combination approaches have been used by Duca *et al*[58] with EC in the aorta and either UW or CEL in the portal vein[58]. In the sample of 72 patients, (36 in UW + EC arm and 36 in CEL + EC arm) both groups had similar patient survival (*P* = 0.55), primary non function (*P* not listed), and initial poor function rates (*P* not listed)[58].

Lower viscosity solutions such as CEL and HTK have been suggested to prevent biliary related complications relative to that of UW. A retrospective review of 256 liver transplants revealed that HTK was superior to UW in protecting against the formation of a biliary anastomotic strictures (OR = 0.40, *P* = 0.005)[19]. Mangus *et al*[44] revealed a lower incidence of biliary sludge associated with the use of HTK compared to UW (*P* = 0.001). These findings were re-iterated by Canelo *et al*[47] who revealed decreased biliary complications associated with the use of HTK compared to UW. In contrast, Rayya *et al*[45], Erhard *et al*[43], and Moench *et al*[59] found no difference in biliary complications between UW and HTK. CEL and HTK represent a useful alternative solution to UW. The moderate cost savings of HTK and potential for

Table 3 Selected clinical studies involving renal preservation solutions

Ref.	Solution	Cases	Patient survival	Graft survival
UW solution *vs* HTK solution				
Lynch *et al*[60]	UW *vs* HTK	Living donor = 950 (UW 475, HTK 475) Deceased donor = 634 (UW 317, HTK 317)	No diff (1 yr) (living or deceased donors)	No diff (1 yr) (Living or deceased donors)
de Boer *et al*[61]	UW *vs* HTK	611 (UW 297, HTK 314)	----	No diff (1 yr) (UW 81%, HTK 83%)
Klaus *et al*[62]	UW *vs* HTK	51 (UW 27, HTK 24)	No diff (1 yr) (UW 84% *vs* HTK 86%)	No diff (1 yr) (UW 78%, HTK 79%)
UW solution *vs* CEL solution				
Montalti *et al*[64]	UW *vs* CEL	50 (UW 25, CEL 25)	No diff (1 yr) (UW 100%, CEL 100%)	No diff (1 yr) (UW 96%, CEL 91.8%) *P* value not stated
Faenza *et al*[23]	UW *vs* CEL	187 (UW 88, CEL 99)	No diff (2 yr) (UW 100%, CEL 100%)	No diff (2 yr) (UW 75%, CEL 84%) *P* value not stated
Pedotti *et al*[54]	UW *vs* CEL	441 (UW 269, CEL 172)	No diff (1 yr) (UW 97.7%, CEL 99.4%) *P* value not stated	No diff (1 yr) (UW 91%, CEL 94.2%) *P* value not stated
EC solution *vs* HTK solutions				
de Boer *et al*[61]	EC *vs* HTK	569 (EC 277, HTK 292)	----	No diff (1 yr) (EC 78%, HTK 80%) *P* value not stated

Diff: Difference; UW: University of Wisconsin; CEL: Celsior; HTK: Histidine-tryptophan-ketoglutarate; EC: Euro-Collins.

reduced biliary complications in some clinical situations (such as donation after cardiac death) are possible benefits for using HTK in liver transplantation.

RENAL PRESERVATION

Studies of UW and HTK have been of great interest in renal transplantation (Table 3). An evaluation of UW to HTK in 950 living donor (475 UW and 475 HTK) and 634 deceased donor (UW 317, HTK 317) renal transplants revealed there was no difference in graft survival or patient survival (*P* not stated)[60]. However, there was a statistically significant increase in the incidence of delayed graft function with the use of UW in living donors (8.2% UW *vs* 3.2% HTK, *P* = 0.001), while the use of HTK was associated with delayed graft function in deceased donors (17.4% UW *vs* HTK 26.2%, *P* = 0.005)[60]. In a separate multi-center randomized trial, 611 patients received either UW (*n* = 297) or HTK (*n* = 314) with no difference observed in one year graft survival (UW 81% *vs* HTK 83%, *P* not stated) or initial non-function rate (33% both groups, *P* not stated)[61]. Similar results were observed by Klaus *et al*[62].

In the same study above, EC was compared to HTK in 569 transplants (277 EC *vs* 292 HTK)[61]. There was no difference in graft survival at one year (78% EC *vs* 80% HTK *P* not stated)[61]. However, an analysis of the initial non-function rate revealed a lower incidence associated with the use of HTK (HTK 29% *vs* EC 43%, *P* = 0.001)[61].

The use of CEL for renal transplants has been investigated. Catena *et al*[63] showed good outcomes in 10 patients with a graft survival of 90% and patient survival of 100% at 1 year. Larger comparison studies involving the use of CEL have also been performed. In a multicenter randomized trial, renal transplantations in the elderly (> 60 years old) were compared in 50 patients (25 UW and 25 CEL)[64]. There were no deaths in either group and no differences with respect to 1 year graft survival (UW 96% and 91.8% CEL, *P* not stated). These findings were congruent with Pedotti *et al*[54] and Faenza *et al*[23] who conducted a prospective randomized study of renal transplants in 187 cases (UW 88, CEL 99). There was no statistical difference in graft survival (UW 75% *vs* CEL 84%, *P* not stated), patient survival (100% in each group, *P* not stated), or graft dysfunction (UW 33.9% *vs* CEL 31.3%, *P* not stated)[23].

Cost analyses of preservation solutions in the setting of renal transplants have been explored. The cost of HTK is lower than identical volumes of UW (UW $322 USD per liter *vs* HTK $148 USD per liter)[65]. These values translated into cost savings of $548 USD (47%) per renal donor by switching from UW to HTK[65]. Likewise, Moray *et al*[66] suggested cost savings during the transition from UW to HTK although the magnitude was not as large ($148 USD per renal transplant)[66].

These studies reveal that UW, HTK, and CEL are equivalent with respect to patient and graft survival. In addition, delayed graft function appears to be comparable for UW, HTK, and CEL and should be discouraged for EC[61,67]. However, the use of HTK may be favored for renal transplants given the potential for cost savings over UW.

PANCREAS PRESERVATION

Several studies have compared UW to HTK in the setting of pancreas transplants (Table 4). Potdar *et*

Table 4 Selected clinical studies involving pancreas preservation solutions

Ref.	Solution	Cases	Patient survival	Graft survival
UW solution *vs* HTK solution				
Potdar *et al*[68]	UW *vs* HTK	33 (UW 17, HTK 16)	No diff (30 d) (UW 100%, HTK 100%)	No diff (30 d) (UW 100%, HTK 94%)
Englesbe *et al*[69]	UW *vs* HTK	75 (UW 41, HTK 36)	No diff (90 d) (UW 100%, HTK 100%)	No diff (90 d) (UW 90.2%, HTK 86%)
Schneeberger *et al*[70]	UW *vs* HTK	68 (UW 41, HTK 27)	No diff (6 mo) (100% UW and HTK 96.3%)	No diff (6 mo) (90.2% UW, 85.2% HTK)
Becker *et al*[71]	UW *vs* HTK	95 (UW 47, HTK 48)	No diff (1 yr) (UW 89.4% and HTK 95.7%)	No diff (1 yr) (UW 82.6%, HTK 85.4%)
Agarwal *et al*[72]	UW *vs* HTK	87 (UW 10, HTK 78)	No diff (1 yr) (UW 100% and HTK 93%)	No diff (1 yr) (UW 100% and HTK 92%)
Alonso *et al*[74]	UW *vs* HTK	97 (UW 81, HTK 16)	No diff (3 yr)	No diff (3 yr)
UW solution *vs* CEL solution				
Manrique *et al*[77]	UW *vs* CEL	72 (UW 44, HTK 28)	No diff (2 yr) (UW 94.7%, CEL 84.4%)	No diff (2 yr) (UW 74.6%, CEL 77.4%)
Boggi *et al*[25]	UW *vs* CEL	100 (UW 50, HTK 50)	No diff (1 yr) (UW 98.0%, CEL 98.0%)	No diff (1 yr) (UW 95.8%, CEL 95.9%)

Diff: Difference; UW: University of Wisconsin; CEL: Celsior; HTK: Histidine-tryptophan-ketoglutarate.

al[68] compared 33 cases and found both graft survival at 1 mo (UW 100% and HTK 94%, $P = 0.49$) and patient survival at 1 mo (100% in both groups) were not statistically different. Englesbe *et al*[69] observed non-inferiority of HTK compared to UW with respect to graft survival (UW 90.2%, HTK 86%, *P* not stated) and patient survival (100% both groups) in 75 patients for a duration of 90 d following surgery. Studies with greater long-term follow-up have revealed that this relationship is consistent at 6 mo and 1 year[70-72].

Graft thrombosis and pancreatitis have been reported with the use of HTK for pancreas transplants. After switching from UW to HTK, a series of 87 pancreas transplants resulted in 3 graft thrombosis (out of 5 total graft failures)[72]. A follow-up study at the same institution with 152 patients, revealed 10 cases of graft failure with 7 resulting from thrombosis (6 venous, 1 arterial)[73]. A direct comparison between UW and HTK in 97 patients found the frequency of pancreatitis (23% UW and 56% HTK, $P = 0.01$) and graft thrombosis (UW 4%, HTK 19%, $P = 0.05$) was higher with the use of HTK[74]. These findings are in contrast to larger series performed by Fridell *et al*[75] who found no differences in outcomes of 308 pancreas transplants with the use of UW and HTK and suggested the differences in other studies may have been attributed to long ischemic times and larger flush volumes.

As with Liver and kidney transplants, a cost analysis revealed that HTK is cheaper than UW and may be preferentially used given this financial advantage[76]. Cost savings of 43% were found with pancreas grafts preserved with HTK rather than UW, despite a higher volume of HTK in this study ($P < 0.01$)[69]. Alonso *et al*[74] suggested the volume of HTK used was substantial enough to result in higher overall costs with a difference of $115 USD per patient relative to UW[74]. However, the volume of HTK was higher than other studies such as Agarwal *et al*[72] (mean 4.9 L *vs* 3.9 L per case, respectively). Additionally, a significant difference between the volume of HTK and UW was present (HTK 4.9 L *vs* UW 2.6 L, $P < 0.01$) which is inconsistent with other studies. Together, these findings may account for the differences observed by Alonso *et al*[74].

Similar to HTK, CEL has been shown to be a viable option to UW for pancreas transplants. Manrique *et al*[77] compared 72 patients and found no difference in graft survival at two years (UW 74.6%, CEL 77.4%, *P* not stated). There was no significant difference in thrombosis (*P* not stated) although there was a trend towards a higher incidence of thrombosis in those patients that received UW (UW 5 and CEL 2, *P* not stated)[77]. This was attributed to the lower number of portocaval anastomosis in the UW group compared to the CEL group[77]. In a study by Boggi *et al*[25] comparing CEL and UW in 100 patients, there was no difference in 1 year graft survival (UW 95.8% and CEL 95.9%, *P* not stated) or 1 year patient survival (98.0% for both groups). These studies suggest that patient survival outcomes are equivalent between CEL and UW.

Overall, UW and CEL remain suitable preservation solutions for pancreas transplantations as most studies do not a show a difference in mortality or graft survival. Limited evidence suggests a potential association of HTK with pancreatitis and graft thrombosis therefore, dissuading its use given the availability of safer alternatives until larger studies can be performed to address this issue.

INTESTINAL PRESERVATION

Despite many improvements in intestinal transplantation, it remains a challenging undertaking. Graft ischemia time is limited to 6-10 h and the available literature suggests that the use of UW is not as effective as other abdominal organs[33]. There is a paucity of human studies to guide the optimal preservation strategy for

intestinal transplantation. Therefore, decisions regarding preservation solutions, in the setting of intestinal transplantation are guided primarily by animal models. Roskott *et al*[33] have proposed that an intraluminal flush with preservation solutions be performed in addition to intra-vascular flush as the most venerable epithelial cells are localized at the apex of the villus which receives nutrition predominantly from absorption in the lumen. A similar approach has also been advocated by Oltean *et al*[78] as a measure to abrogate mucosal integrity and bacterial translocation. Overall, the lack of clinical data prevents a definitive determination of the optimal solution in intestinal transplants. It appears that UW or HTK infused intraluminally in conjunction with an intra-vascular washout is the best strategy at this time in optimizing intestinal integrity during the *ex-vivo* period.

CONCLUSION

The advancement of transplantation has occurred, in part, to thoughtful scientific endeavors aimed at optimizing preservation solutions and diligent clinical endeavors. Notable differences exist between preservation solutions with respect to the composition of electrolytes, impermeants, buffers, antioxidants, and energy precursors have evolved. Based upon the aforementioned studies, meaningful evidence exists to guide effective organ preservation strategies in many cases while potentially ameliorating high healthcare costs. CEL and HTK are likely non-inferior to that of UW in the setting of renal, liver, and pancreas transplantats in terms of graft and patient survival. Parsons *et al*[79] have also suggested equivalence between UW, HTK, and CEL for abdominal transplants. As such, the use of a single preservation solution for abdominal as well as thoracic transplantation has been proposed[80]. From a cost perspective, UW remains relatively expensive therefore, switching to alternatives such as HTK in renal and hepatic transplantation may yield a financial benefit for some centers as well as the potential for a reduced number of biliary complications in liver transplantation. However, the use of HTK is cautioned in pancreas transplants given the potential for pancreatitis and thrombosis as some studies have revealed. Given equivocal patient and graft survival, UW or CEL usage may be preferred in such settings. Intestinal transplantation remains in its infancy however, as the volume and experience with this procedure continues, research into the optimal preservation strategies will be needed. While it is important to strive to make informed decisions supported by evidence based data to promote graft function and survival, many variables affect these outcome measures and are not always accounted for by these clinical studies. Focusing on preservation solutions represents one potential avenue to improve patient and graft outcomes in transplantation and may be an effective strategy to decrease healthcare costs associated with transplantation.

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