

Histidine-Tryptophan-Ketoglutarate for Pancreas Allograft Preservation: The Indiana University Experience

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Histidine-tryptophan-ketoglutarate solution (HTK) has been scrutinized for use in pancreas transplantation. A recent case series and a United Network for Organ Sharing data base review have suggested an increased incidence of allograft pancreatitis and graft loss with HTK compared to the University of Wisconsin solution (UW). Conversely, a recent randomized, controlled study failed to show any significant difference between HTK and UW for pancreas allograft preservation. This study was a retrospective review of all pancreas transplants performed at Indiana University between 2003 and 2009 comparing preservation with HTK or UW. Data included recipient and donor demographics, 7-day, 90-day and 1-year graft survival, peak 30-day serum amylase and lipase, HbA1c and C-peptide levels. Of the 308 pancreas transplants, 84% used HTK and 16% UW. There were more SPK compared to pancreas after kidney and pancreas transplant alone in the HTK group. Donor and recipient demographics were similar. There was no significant difference in 7-day, 90-day or 1-year graft survival, 30-day peak serum amylase and lipase, HbA1c or C-peptide. No clinically significant difference between HTK and UW for pancreas allograft preservation was identified. Specifically, in the context of low-to-moderate flush volume and short cold ischemia time (≤ 10 h), no increased incidence of allograft pancreatitis or graft loss was observed.

Key words: HTK solution, pancreas transplantation, preservation solutions, University of Wisconsin solution

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Introduction

Preservation solutions are used to maintain an organ intended for transplantation in optimal condition from the time of procurement until reperfusion at transplantation.

The use of these solutions offers many advantages and has been considered one of the major advances in modern organ transplantation. The University of Wisconsin solution (UW) is currently the most commonly used preservation solution for abdominal organ transplantation and the standard to which newer solutions are compared. This solution contains osmotic effective substances lactobionate, raffinose and hydroxyethyl starch combined with a phosphate buffer and high potassium (Table 1). Histidine-tryptophan-ketoglutarate solution (HTK), developed in the 1970s by Bretschneider as a cardioplegia solution (1), is being used at many centers as an alternative to UW for abdominal organ preservation (2). HTK, like UW, is similar in electrolyte content to intracellular fluid because it contains a low concentration of sodium (Na^+ 15 mM) in order to prevent Na^+ and water influx into the cell during ischemia, and therefore decrease cellular swelling (Table 1). In contrast to UW, HTK maintains a low potassium concentration so that it can safely be released into the circulation. Histidine is included for its substantial buffering capacity to slow the drop in pH during conditions of anaerobic metabolism. It also demonstrates good penetration from the intravascular to the interstitial space but has low penetration intracellularly to avoid edema. Tryptophan is included in HTK as a membrane stabilizer, ketoglutarate as an energy substrate and mannitol as an oxygen-free radical scavenger. Perhaps the most noticeable characteristic is the very low viscosity of HTK (similar to that of water at 1–35°C) leading to a rapid flow rate (three times that of UW) with quicker exsanguination and cooling of organs. The manufacturer of HTK recommends a high-volume flush (8–10 L), or alternatively at least 10 min of flushing at the time of organ procurement. This was believed to optimize electrolyte equilibration across the cell membrane and ensure that the extracellular fluid is completely replaced with preservation solution (3). Clinical experience has demonstrated that this is actually not necessary and many programs, including our own, have suggested that this may actually be detrimental for pancreas preservation (4–6). Indiana University has adopted the principle of flushing the organs until the effluent is clear, as we had historically done with UW. Our current flush volume for HTK (3.8–4.0 L) is statistically similar to our prior flush volume for UW (3.2–3.4 L) (7–9).

HTK has recently been scrutinized for use in pancreas transplantation. A recent two-center case series (6)

Table 1: Constituents of the University of Wisconsin (UW) and histidine-tryptophan-ketoglutarate (HTK) solutions

Component	UW (mM)	HTK (mM)
Na	30	15
K	120	9
pH	7.4	7.1
Lactobionate	100	
Glutathione	3	
Raffinose	30	
Hydroxyethyl starch	5 gm%	
Adenosine	5	
Histidine		180
Tryptophan		2
Ketoglutarate		1
Mannitol		30

suggested an increased risk of allograft pancreatitis and thrombosis for HTK preserved grafts, and a UNOS data base review (10) reported an increased risk of graft loss for HTK when compared to UW. Conversely, a recent randomized, controlled trial failed to show any significant difference between HTK and UW for pancreas allograft preservation (11). The present study reviews and updates the largest single-center experience with HTK for pancreas allograft preservation, and compares allografts preserved with HTK or UW.

Materials and Methods

This was a retrospective review of all pancreas transplants performed at Indiana University Hospital between 2003 and 2009 (n = 308). All local procurements used HTK primarily as of May 2003. Our center routinely uses an HTK flush volume of 3–4 L. All recipients were listed for transplantation according to standard procedures and protocols as established by the United Network for Organ Sharing (UNOS). Pancreas allografts were typically procured using an en-bloc technique following aortic flush with preservation solution and topical cooling with saline slush as previously described (7,8,12). The recipient operation was performed through a midline incision. The pancreas was routinely positioned with the tail toward the pelvis and the head and duodenum oriented superiorly in order to facilitate the enteric anastomosis. Systemic venous drainage was performed to the right common iliac vein or to the vena cava. Arterial perfusion of the allograft was established from either the right or left common iliac artery. All simultaneous pancreas and kidney (SPK) transplants were performed with ipsilateral placement of both the kidney and the pancreas to the right iliac vessels as previously described (13). All pancreas allografts were drained enterically using a stapled technique as described elsewhere (14). Routine immunosuppression in all recipients consisted of induction with five doses of rabbit antithymocyte globulin (rATG) (1 mg/kg/dose), early steroid withdrawal and maintenance with tacrolimus (target trough level of 8–10 ng/mL) and sirolimus (target trough level of 3–6 ng/mL) (15,16). In certain situations where the side effects of the maintenance immunosuppression were not well tolerated, mycophenolate mofetil (MMF) was either added in order to decrease the dosage of all three medications, or used instead of sirolimus.

The focus of this study was early pancreas graft function. Research variables and outcomes included recipient and donor demographics, 7-day, 90-day and 1-year graft survival, peak 30-day serum amylase and lipase levels, HbA1C and c-peptide. Standard statistical techniques were employed

using commercially available software (SPSS 17.0 for Windows, SPSS Inc., Chicago, IL). Bivariate statistical testing was performed using chi-square and analysis of variance (ANOVA) for categorical and continuous variables, as indicated. Cox proportional hazards survival modeling was utilized for analysis of survival and a direct entry method was used for statistically significant covariates. Covariates with a p-value ≤ 0.10 were included in the final model. All pancreas transplants performed during the study period were included in the analysis. Specifically, there were no exclusions for technical graft loss or graft loss or patient death not related to the transplant procedure. Use of data from the transplant center data base for deidentified, retrospective analysis has been reviewed and approved by the institutional review board of the Indiana University School of Medicine.

Results

Of the 308 pancreas transplants 258 (84%) were preserved with HTK and 50(16%) with UW (Table 2). The types of transplants were 172 SPK, 74 pancreas after kidney (PAK) and 62 pancreas transplant alone (PTA). There were more SPK compared to PAK and PTA in the HTK group (HTK: 62% SPK, 22% PAK, 15% PTA; UW 22% SPK, 34% PAK, 44% PTA). This difference in transplant type for the two study groups exists because a majority of the SPK were from local donors flushed with HTK, while a majority of the UW group were isolated pancreas allograft imports (PAK or PTA) procured by surgeons from other centers that primarily use UW (Table 2) (17). Demographics between the two groups were similar for donor and recipient age, race, gender and BMI, and for donor peak serum amylase and lipase. Median total ischemic times were similar (HTK 8 h, UW 9 h, $p = 0.46$). Median follow-up was similar (HTK 38 months and UW 34 months). There was no significant difference in 7-day or 90-day graft loss or 1-year graft survival (HTK 92%, UW 86%, $p = 0.26$) (Table 3 and Figure 1), 30-day peak serum amylase (HTK 216, UW 163, $p = 0.17$) or lipase (HTK 156, UW 126, $p = 0.68$) (Figure 2), median HbA1C (HTK 5.4, UW 5.5, $p = 0.51$) or median c-peptide (HTK 2.4, UW 2.4, $p = 0.63$).

Discussion

Since the introduction of HTK in clinical transplantation over 20 years ago, thousands of patients around the world have received HTK-preserved transplant allografts. Initial evaluation of the safety and efficacy of HTK was conducted on a large scale with a well- designed multicenter, randomized, controlled trial conducted between 1990 and 1993 among kidney transplant recipients in Europe (18). Based upon this study and others, HTK was accepted for use in the United States in 2001. Additional quality randomized, controlled trials have been conducted comparing HTK to UW in liver and pancreas transplantation demonstrating clinical equivalence in all cases (11,19,20). Many large single-center case series have also been published which have supported the claim of clinical equivalence between HTK and UW in kidney, pancreas, liver and intestinal transplantation (7,9,21–26).

Table 2: Demographic data for pancreas transplant recipients and corresponding donors stratified by the preservation solution for the donor graft (HTK or UW)

Overall	Overall 308 (100%)	HTK (%) 258 (84%)	UW (%) 50 (16%)	p-Value
RECIPIENT				
Transplant type*				<0.001
SPK	56%	62%	22%	
PAK	24%	22%	34%	
PTA	20%	15%	44%	
Gender				0.87
Male	61%	62%	60%	
Race				0.48
White	91%	91%	92%	
Black	7%	7%	4%	
Other	2%	2%	4%	
Age				0.53
Mean, median (years)	42.6, 43	42.8, 42	41.9, 43	
Body mass index				0.28
Mean, median	25.4, 24.4	25.3, 24.4	26.0, 24.7	
Retransplant	8%	8%	4%	0.39
Donor				
Gender				0.6
Male	64%	65%	61%	
Race				0.79
White	80%	80%	78%	
Black	14%	13%	17%	
Other	6%	7%	5%	
Age				0.61
Mean, median (years)	26.4, 24	26.2, 24	27.2, 25	
Body mass index				0.8
Mean, median	24.4, 24.0	24.4, 24.1	24.2, 23.7	
Serum amylase (mean, median)				
First	125, 67	120, 67	159, 66	0.22
Peak	154, 75	145, 78	204, 73	0.12
Serum lipase (mean, median)				
First	83, 29	88, 30	51, 24	0.11
Peak	92, 33	94, 34	73, 26	0.42
Transplant data				
Total ischemia time				0.01
Mean, median (hours)	8.4, 8	8.3, 8	9.3, 9	
Regional origin of graft				<0.001
Local	70%	81%	12%	
Import	30%	19%	88%	
Procuring surgeon				<0.001
Program surgeon	74%	81%	34%	
Non-program surgeon	26%	19%	66%	

*Transplant type: SPK, simultaneous pancreas and kidney transplant; PAK, pancreas transplant after previous kidney transplant; PTA, pancreas transplant alone.

Preservation solution: HTK is histidine-tryptophan-ketoglutarate preservation solution; UW is University of Wisconsin preservation solution.

The first published report of successful pancreas transplantation using HTK flush and preservation was from Indiana University in 2004 (12). Ten pancreas allografts preserved in HTK were compared to the prior 10 allografts stored in UW. There was no difference in allograft survival, glucose homeostasis or serum amylase levels. These data have been updated twice (7,8). Of note, the mean volume of HTK flush was 3.9 ± 1.0 L and the mean cold ischemic time was 8 h. Potdar et al. reported the initial

experience with pancreas preservation in HTK at the University of Pittsburgh Medical Center (5). In that report, 16 grafts were flushed with HTK and 17 with UW. The flush volume was routinely 8–10 L for HTK compared to 4–5 L for UW. Cold ischemic time was 14–15 h. In this particular study, the authors noted subjectively more parenchymal edema and significantly higher day 1 amylase and lipase levels in HTK flushed grafts. There was no difference in graft survival, complication rates or day 10 amylase or

Table 3: Posttransplant outcomes data for 308 consecutive pancreas transplant recipients stratified by preservation solution (HTK or UW)

Number	Overall (%) 308 (100%)	HTK (%) 258 (84%)	UW (%) 50 (16%)	p-Value
Graft loss within 7 days	4%	3%	8%	0.11
Graft loss within 90 days	7%	6%	12%	0.12
1-year* (n=269)				
Graft survival	91%	92%	86%	0.26
Patient survival	97%	96%	98%	0.66
Months follow-up (median)	37	38	34	0.46
Readmission within 3-months	50%	51%	44%	0.35
30-day post-transplant peak (median)				
Serum amylase	201	216	163	0.17
Serum lipase	154	156	126	0.68
Most recent HbA1c (mean, median)	5.6, 5.4	5.6, 5.4	5.5, 5.5	0.51
Most recent C-peptide (mean, median)	2.7, 2.4	2.7, 2.4	2.9, 2.4	0.63

*For patients with minimum of 1-year follow up time.
HTK is histidine-tryptophan-ketoglutarate preservation solution
UW is University of Wisconsin preservation solution

lipase levels. Englesbe et al. reported a multicenter study comparing 36 HTK and 41 UW preserved pancreas allografts transplanted at four centers in Michigan (23). In this case, the flush volume of HTK was 5 L. Cold ischemic times were 7.7 h for UW and 9.5 h for HTK. There was no difference in graft survival between the two groups and a difference in peak serum amylase or lipase levels was not demonstrated. In another recent publication by Becker et al. from the Medical School of Hannover, 48 HTK preserved pancreas allografts were compared to 47 UW preserved grafts (22). Since 1992, when Gubernatis et al. published the initial clinical experience with this preservation solution in liver transplantation (27,28), this program has been using HTK exclusively. For this reason, all UW preserved grafts were imported and had a slightly longer

cold ischemic time (12 h compared to 10 h for HTK). The flush volume was 9.6 ± 2 L for HTK and 4.8 ± 1 L for UW. There was no statistically significant difference in graft survival or serum peak amylase or lipase levels. The current study at Indiana University is the largest reported series of pancreas allografts preserved in HTK (n = 258) and again demonstrates no clinically significant difference in graft survival or function.

The consistency of published studies reporting clinical equivalency for HTK and UW has recently been challenged in several articles recently published in the American Journal of Transplantation. Alonso et al. reported a case series of 97 pancreas transplants performed at two different centers between 2001 and 2007 (16 HTK, 81 UW) (6). The

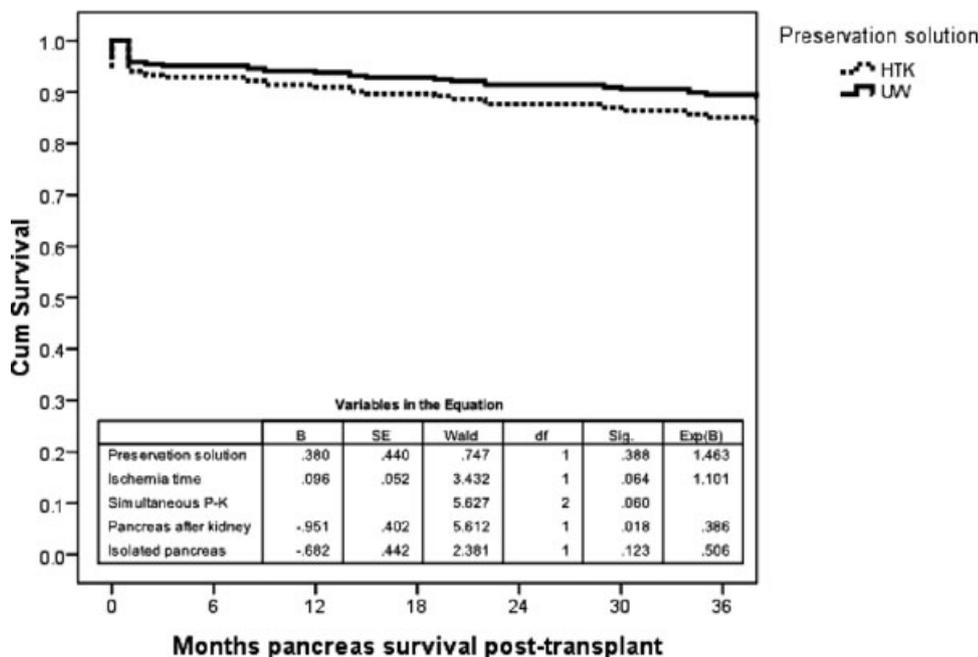


Figure 1: Cox proportional hazards model for pancreas graft survival in 308 consecutive pancreas transplants comparing grafts preserved in histidine-tryptophan-ketoglutarate solution (HTK) and the University of Wisconsin solution (UW) (p = 0.39).

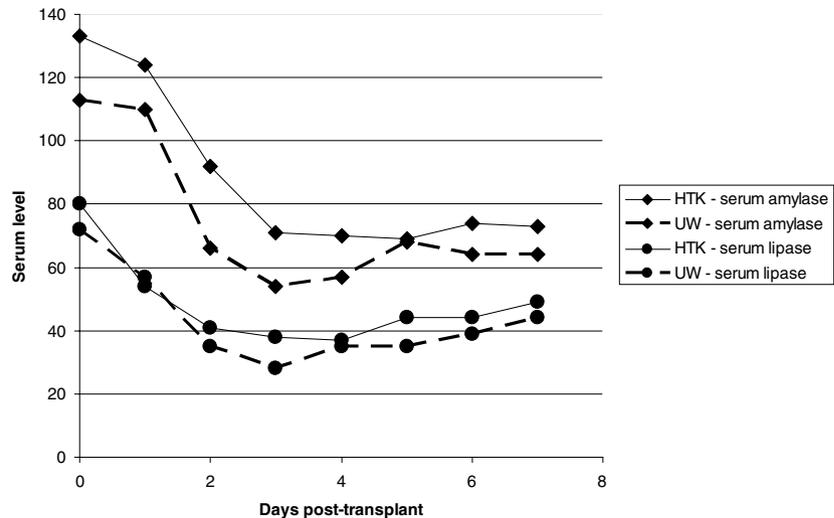


Figure 2: Posttransplant amylase and lipase stratified by organ preservation solution (HTK or UW) (n = 308).

findings included a significantly higher graft pancreatitis rate (56% vs. 23%), thrombosis rate (19% vs. 5%) and peak serum amylase level in the 16 consecutive grafts preserved in HTK when compared to those preserved with UW (n = 81). Patient and graft survival were not statistically different. The mean flush volume was 4.9 ± 1 L for the 16 pancreas grafts flushed with HTK solution, but for the three grafts that thrombosed the mean flush volume was 5.53 ± 1 L. The mean cold ischemia time for the HTK group was 13.9 ± 4.7 h. Data regarding specific ischemia times for the three thrombosed grafts were not provided. The finding of increased allograft pancreatitis had previously been suggested in other publications (5,29), but the possibility of increased rate of graft thrombosis was raised as a new concern based on this study. Subsequently, Stewart et al. conducted three retrospective analyses using the UNOS data base to compare HTK and UW preservation for deceased donor kidney, liver, and pancreas transplants performed from July, 2004, through February, 2008 (10,30,31). In pancreas transplantation, after adjusting for other donor, recipient, graft and transplant factors, HTK preservation (n = 1081) was independently associated with an increased risk of pancreas graft loss (HR 1.30, p = 0.014), especially with cold ischemia times beyond 12 h (HR 1.42, p = 0.017) when compared to UW preservation (n = 3311). Moreover, HTK preservation was associated with a higher risk of early (<30 days) pancreas graft loss (OR 1.54, p = 0.008). Contrary to the reasonably compelling data presented in these publications, a prospective randomized controlled multicenter study comparing HTK (n = 27) to UW (n = 41) for pancreas allograft preservation from Schneeberger et al. demonstrated no difference in serum amylase, lipase, c-peptide, HbA1C or graft survival (11). The preservation flush volume was 5–8 L and the cold ischemia time was 10.8 ± 3.7 h for the HTK group. Of note, the only two cases of allograft thrombosis were in the UW group, whereas there was one severe pancreatitis leading to allograft loss from bleeding in the HTK group.

Overall, safe pancreas preservation with HTK solution has been demonstrated by our group at the Indiana University, but this was specifically achieved with low flush volumes and short cold ischemia times. It is important to realize that the mean ischemic time, whether the pancreas was from a local donor or was imported from across the country, was <10 h (17). With higher flush volumes (>5 L) and longer ischemic times (>12 h), there may be a risk of allograft pancreatitis as suggested in the reports by Alonso and Stewart (6,10). The decision to use HTK for pancreas preservation should be individualized based on transplant center practices. Previous research suggests that care must be taken not to overflush the pancreas allograft with any preservation solution as this may lead to allograft edema and pancreatitis and there seems to be a clear benefit to maintaining as brief a cold ischemia time as possible.

Conclusion

No clinically significant difference between HTK and UW for pancreas allograft preservation was identified. Specifically, in the context of 3–4 L flush volume and short (≤ 10 h) cold ischemia time no increased incidence of allograft pancreatitis or graft loss was observed.

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