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ORIGINAL ARTICLE

A prospective randomized multicenter trial comparing histidine–tryptophane–ketoglutarate versus University of Wisconsin perfusion solution in clinical pancreas transplantation

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Summary

We aimed to evaluate early pancreas transplant graft function after histidine–tryptophan–ketoglutarate (HTK) versus University of Wisconsin (UW) perfusion. Prospective randomized multicenter study including 68 pancreas transplantations stratified according to preservation fluid used (27 HTK vs. 41 UW). Primary endpoint was pancreas graft survival at 6 months. Serum α-amylase, lipase, C-peptide, HbA1C and exogenous insulin requirement were compared at several time points. Mean pancreas cold ischemia time was 10.8 ± 3.7 (HTK) vs. 11.8 ± 3.4 h (UW) ($P = 0.247$). Simultaneous pancreas–kidney transplantation was performed in 95.6% of the patients, pancreas transplantation alone in 2.9%, and pancreas after kidney transplantation in 1.5%. Six months graft survival was 85.2% (HTK) vs. 90.2% (UW) ($P = 0.703$). Serum amylase and lipase values did not differ between both the groups during the observation period. C-peptide levels were elevated in both the groups without significant differences at each time point. Higher exogenous insulin requirement early after transplantation in the UW group had resolved at 3 months. Six month patient survival was 96.3% (HTK) vs. 100% (UW) ($P = 0.397$). With a mean cold ischemia time of 10 h in this study, HTK and UW solutions appear to be equally suitable for perfusion and organ preservation in clinical pancreas transplantation.

Introduction

Graft preservation during ischemic organ storage is based on hypothermia, which is achieved by topical cooling and cold *in situ* flushing (4 °C), using special perfusion solutions designed to attenuate the effects of ischemia/reperfusion and hence prolong cold ischemia tolerance. More than the case with other abdominal organs, the success in clinical pancreas transplantation is based on careful organ handling and optimal preservation.

For pancreas transplantation, University of Wisconsin (UW) solution is the most commonly used perfusate and is still the reference solution for pancreas preservation [1,2]. UW solution, developed by F.O. Belzer and J.H. Southard, is based on a high osmotic concentration maintained by metabolically inert substances, together with

hydroxyethylstarch as an additional colloid carrier, a phosphate buffer, high potassium and oxygen radical scavengers. Over the last several years, histidine–tryptophan–ketoglutarate (HTK) solution, which was originally designed as a cardioplegic solution in the late 1960s by Bretschneider [3] has been increasingly used for abdominal organ procurement. This solution is based on a potent buffer system (histidine), together with two substances, tryptophan (cell membrane stabilization) and ketoglutarate (anaerobic metabolism substrate). In contrast to UW solution, HTK contains a low concentration of potassium, has a low viscosity, and is used at a low flow rate with a large total volume to achieve equilibrium. On the basis of experimental data [4,5] factors weighing in favor of the use of HTK in pancreas transplantation were lower viscosity and lower costs as compared with UW. Clinical data on HTK in pancreas transplantation have so far been limited to retrospective reports from centers, which have switched from UW to HTK for multi-organ perfusion [6–10]. However, to date, no prospective study comparing both perfusion solutions has been published. Aim of this study was to prospectively evaluate early graft function in clinical pancreas transplantation after organ perfusion with HTK versus UW solution.

Materials and methods

The study was conducted as a prospective randomized multicenter trial including four major academic transplant centers in three European countries. The study protocol had been approved by the local institutional review boards of all participating institutions, and had been registered at ClinicalTrials.gov (http://www.ClinicalTrial.gov).

Aim of the study was to evaluate the outcome of HTK versus UW perfusion for organ protection during organ procurement and storage in clinical pancreas transplantation. Primary study endpoint was pancreas graft survival at 6 months. Normal graft function was defined as normoglycemia (blood glucose levels < 130 mg%) without exogenous insulin requirement, partial function as a C-peptide positive viable graft requiring exogenous insulin. To evaluate the effect of reperfusion injury on early endocrine function, additional secondary endpoints were measured: Serum α-amylase, serum lipase, C-peptide, HbA1C and exogenous insulin requirement were evaluated at six different time points throughout the observation period: 1 = first postoperative day (pod), 2 = pod 3, 3 = pod 10, 4 = 3 weeks after transplantation, 5 = 3 months after transplantation and 6 = 6 months after transplantation. Three weeks after transplantation, an oral glucose tolerance testing was performed in all patients.

After allocation, multi-organ donors were randomized to receive a standard volume of 5000–8000 ml of HTK-solution (HTK group), or 3000 ml of UW solution (UW group) for abdominal organ perfusion. Each of the four participating centers agreed to enroll a defined number of patients, and randomization within each site was center-specific, with the final goal to randomize 120 patients into two equal treatment groups.

Enrollment period was 18 months with a follow-up period of 6 months. All patients undergoing pancreas transplantation were considered for study inclusion. While in general, only type I diabetic patients were considered, a small number of C-peptide negative type II diabetic patients were also included. The inclusion criteria were defined as (i) brain-dead, heart-beating organ donor, (ii) donor age between 10 and 50 years, (iii) donor body mass index < 30 kg/m^2, (iv) pancreas cold ischemia time < 20 h, and (v) written informed consent of the pancreas recipient to participate in the study. Donor serum amylase and serum lipase levels had to be within normal ranges. Exclusion criteria were defined as (i) missing written consent, (ii) pancreas re-transplantation, and (iii) recipient participation in another study.

The study was designed as a phase III study for Germany (phase IV for Austria). After enrollment of about half of the projected study population, HTK was approved for multi-organ perfusion in organ procurement in Germany, and further enrollment of new patients was stopped by the steering committee. Therefore, the study was completed only with the patients included up to the time-point of premature termination.

Perfusion fluids used

The two perfusion fluids used in this study largely differ by ingredients and osmolarity. UW solution is a potassium-rich, sodium-depleted, osmotically active fluid, comparable to the intracellular ion equilibrium. HTK contains only low quantities of either potassium or sodium, and is a crystalloid fluid with an osmolarity only slightly higher than the plasma of the intercellular space.

Perfusion technique

During organ procurement, the surgical approach to *in situ* perfusion of the abdominal organs was similar in both the groups according to standard techniques [11]. Perfusion cannulae of at least 18 Ch were used for retrograde aortic perfusion (perfusion time 8–10 min). Both solutions differed by the amount of perfusion volume used: While in the UW group, 3000 ml perfusion solution was used in the HTK group, 5000–8000 ml (center preference) was given.

Immunosuppression

Immunosuppression was according to center-specific standard protocols, based on an induction therapy, followed by a triple drug regimen with tacrolimus, mycophenolate mofetil and a tapering dose of steroids.

Adverse events

Adverse events were classified according to intensity (mild, moderate, severe), and causality related to the perfusion fluid used (certain/probable/possible/unlikely/not related/unclassifiable). Adverse events were classified as severe if they were associated with patient death, permanent disability, acute threat of life, or resulted in inability to work, malignant disease, or required either readmission or prolonged length of hospital stay. Pancreas graft pancreatitis was defined as elevated pancreas serum enzyme levels, increased need for exogenous insulin with or without regional discomfort over the transplanted organ. Diagnosis of rejection was on the basis of clinical assessment (i.e. increased need for exogenous insulin, fever, malaise), as well as by indirect confirmation of graft rejection by renal allograft histology in patients receiving SPK, i.e. kidney from the same donor together with pancreas.

Statistics

Patient data were reported as mean ± standard deviation or total numbers (%). Analysis was based on comparison of both treatment groups with categorical variables using Fisher's exact test, and numeric data using Wilcoxon–Mann–Whitney test. Significance was assumed if $P \leq 0.05$.

Results

Patient characteristics/organ preservation

A total of 68 pancreas transplants were included in the study, 41 (60.3%) were perfused with UW solution (UW group), and 27 (39.7%) with HTK solution (HTK group). Mean pancreas cold ischemia time was comparable between both the groups: UW 11.8 ± 3.4 h (range 6–19 h) vs. HTK 10.8 ± 3.7 h (range 5–20 h) ($P = 0.247$). Mean recipient age was UW 44.2 ± 8.5 years and HTK 43.0 ± 8.4 years ($P = 0.516$) with a female:male ratio of 1:1.78 (UW) vs. 1:2.86 (HTK) ($P = 0.199$).

Indication for transplantation was type I diabetes in 64 patients (94.1%, UW 40 vs. HTK 24), and type II diabetes in four patients (5.9%, UW one patient versus HTK three patients) ($P = 0.558$), with a median duration of diabetes of 28.9 ± 9.1 years.

Chronic renal failure was associated in 66 patients (97.2%), and 46 patients (67.6%) were on dialysis at time of transplantation. Twelve of them were on peritoneal dialysis, while 32 were on hemodialysis. One patient had undergone a previous successful kidney transplantation. In 65 patients, the kidney from the same donor was transplanted together with the pancreas (SPK), two patients received a pancreas transplant alone (PTA) and one patient a pancreas after successful kidney transplantation (PAK). Systemic venous and enteric drainage of the exocrine pancreas was performed in all pancreas transplantations.

Patient survival

Sixty-seven patients (98.5%, UW 41/41 vs. HTK 26/27) were alive at the end of the study. One HTK patient died, the cause being suicide, 3 months after transplantation with a functioning graft following an uncomplicated postoperative course.

Pancreas graft survival

The primary study endpoint, 6 months post-transplant graft survival, was reached by 37/41 (90.2%) patients in the UW group vs. 23/27 (85.2%) patients in the HTK group ($P = 0.703$) (Fig. 1). Three patients were lost to follow-up (4.4%, one UW versus two HTK). In the UW group, one patient (1.5%) showed a partial pancreas graft function and required low doses of exogenous insulin, and two patients lost their grafts because of venous thrombosis and irreversible rejection respectively. In the HTK group, three patients lost their grafts because of pancreatitis, chronic rejection and death with a functioning graft (suicide), for a total graft loss rate of five patients (7.4%) within the first 6 months post-transplant. No patient underwent re-transplantation within the study period. During the study period, two episodes of acute rejection occurred (2.9%), one in the UW and one in the HTK group, one of which (UW patient) resulted in late graft failure at 6 months.

Pancreas graft function

Serum amylase (Fig. 2) and lipase (Fig. 3) levels at each time point were not significantly different between both the groups. Mean serum lipase and amylase values constantly decreased over time but remained slightly elevated throughout the study period in both the groups. Fasting blood glucose levels and C-peptide levels did not differ significantly at any time point between both the groups. C-peptide levels are listed in Fig. 4. While levels were above normal, there was no difference between the groups; 6 months after transplantation, C-peptide levels were within normal range in all patients.

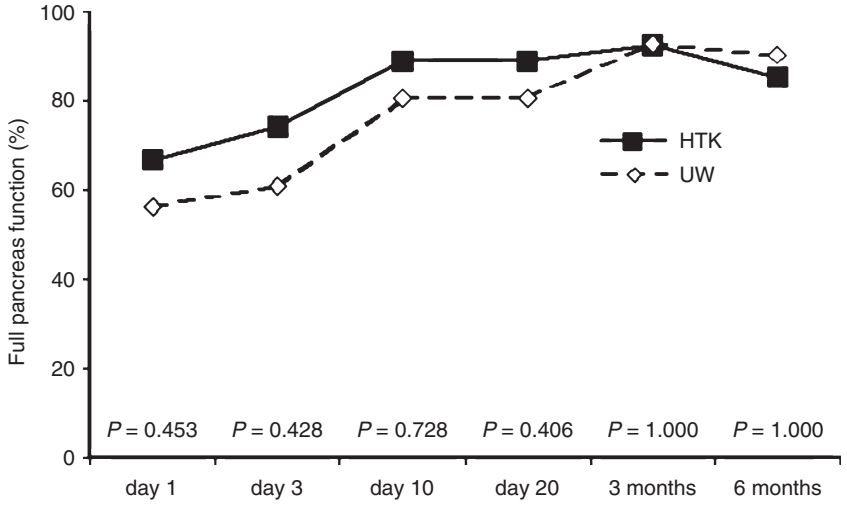

Figure 1 Normal endocrine function (no need for exogenous insulin) for patients with organs perfused with HTK (n = 27) versus UW (n = 41) solution during the first 6 months after pancreas transplantation (mo, months).

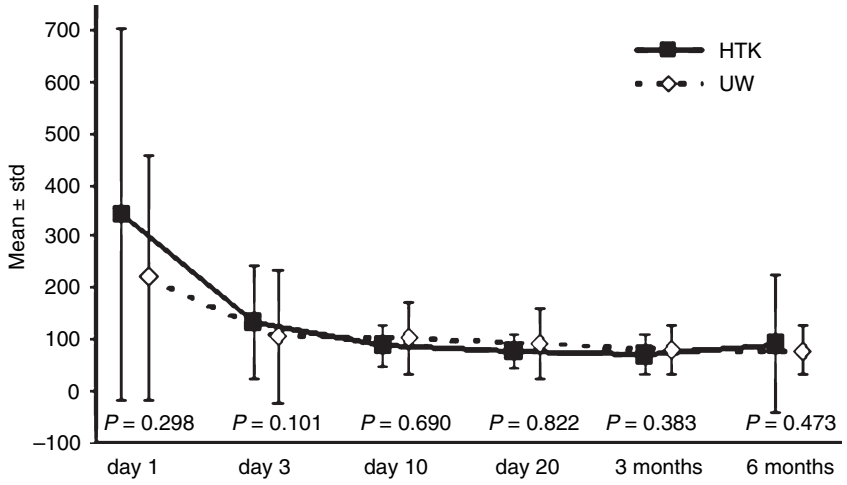

Figure 2 Serial serume amylase levels (U/l) for patients with organs perfused with HTK (n = 27) versus UW (n = 41) solution during the first 6 months after pancreas transplantation (std, standard deviation; mo, months).

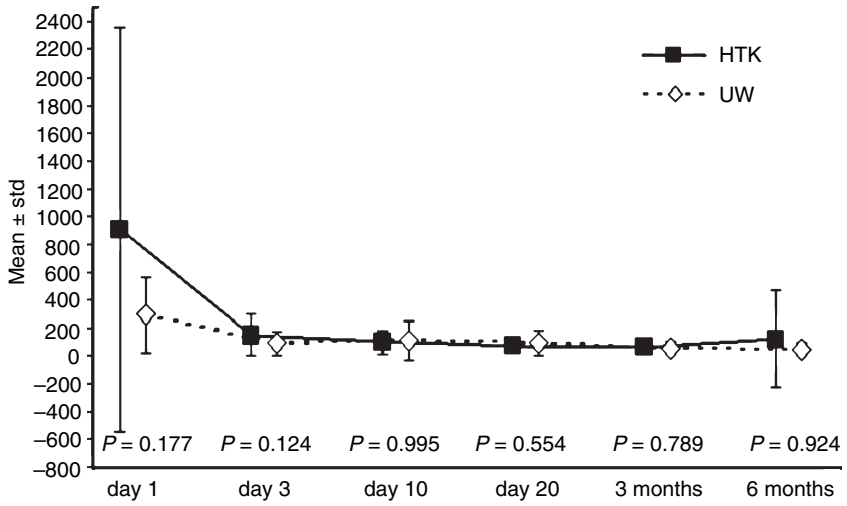

Figure 3 Serial serume lipase levels (U/l) for patients with organs perfused with HTK (n = 27) versus UW (n = 41) solution during the first 6 months after pancreas transplantation (std, standard deviation; mo, months).

Need for exogenous insulin to maintain normoglycemia (<130 mg%) is depicted in Fig. 5. Beginning from pod 1, more patients in the UW group required exogenous insulin as compared with the HTK group [UW 27 (67.5%) vs. HTK 11 (40.7%); P = 0.044]. In addition, patients in the UW group showed higher insulin requirement on

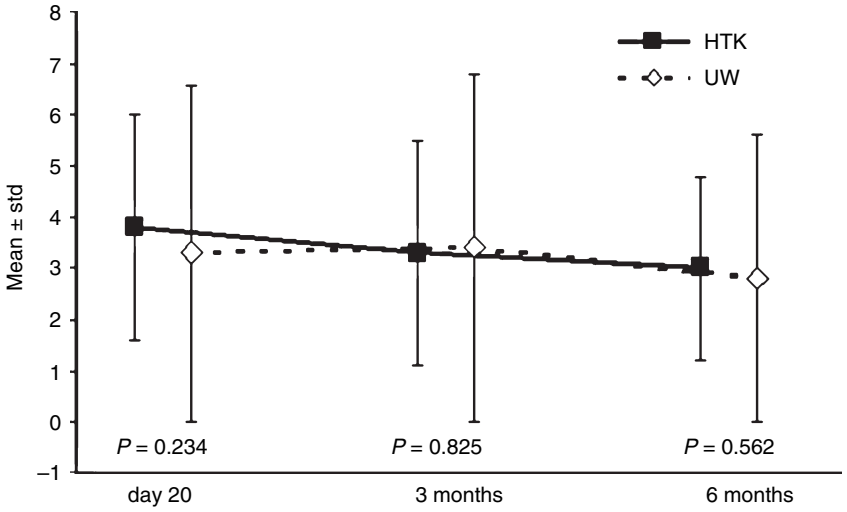

Figure 4 C-peptide levels (ng/ml) 20 days, 3 and 6 months after pancreas transplantation for patients with organs perfused with HTK (n = 27) versus UW (n = 41) solution (std, standard deviation; mo, months).

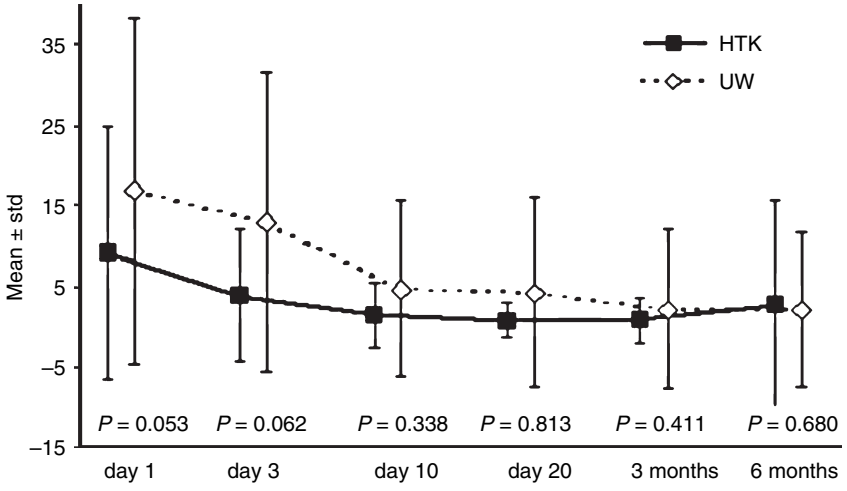

Figure 5 Mean amount of daily exogenous insulin (IE) for patients with organs perfused with HTK (n = 27) versus UW (n = 41) solution during the first 6 months after pancreas transplantation (std, standard deviation; mo, months).

day 1 (P = 0.053) and day 3 (P = 0.062), which resolved by postoperative month 3 (Fig. 5). At 6 months, there was no difference between both the groups.

Three weeks after transplantation, results of oral glucose tolerance testing were comparable between the groups (UW versus HTK; P = 0.317) and HbA1c levels 3 weeks (UW 6.7 ± 0.8 vs. HTK 6.7 ± 0.9; P = 1.000), 3 months (UW 5.5 ± 0.5 vs. HTK 5.6 ± 0.6; P = 0.338) and 6 months (UW 5.6 ± 0.6 vs. HTK 5.6 ± 0.5; P = 0.704) post-transplant were not different (Fig. 6).

Kidney graft survival

At 6 months after transplantation, four (three UW and one HTK) of 65 patients undergoing simultaneous pancreas–kidney transplantation were lost to follow-up (5.9%). One HTK patient lost his graft attributable to primary nonfunction. All other patients (60/61; 98.3%) were off dialysis. Serum creatinine levels were within normal ranges in all UW patients and elevated in two (7.4%) HTK patients. One acute rejection episode (1.5%) occurred in a HTK patient.

Adverse events

A total of 77 adverse events were reported (UW 33 vs. HTK 44) in 14 patients [7 (17.1%) UW vs. 7 (25.9%) HTK]. Median adverse event duration in the UW group was 6 days (0–54) vs. 5.5 days (0–47) in the HTK group. Event severity was mild in 55.8% and moderate in 32.5%, and was not classified in three cases (3.9%). Six (7.8%) severe adverse events [UW 2 (6.1%) vs. HTK 4 (9.1%)] were reported, including two cases of graft thrombosis (one complete venous thrombosis leading to graft loss, one partial splenic vein thrombosis) in the UW group and one suicide, one severe graft pancreatitis with arterial

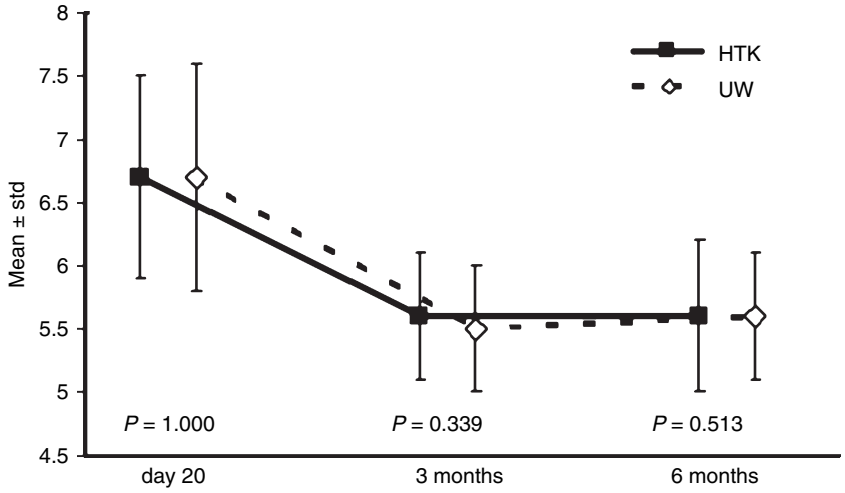

Figure 6 Mean HbA1c blood levels for patients with organs perfused with HTK (n = 27) versus UW (n = 41) solution during the first 6 months after pancreas transplantation (std, standard deviation; mo, months).

bleeding and subsequent graft loss, and two cases of small bowel obstruction in the HTK group.

A single event in the UW group (complete pancreas graft vein thrombosis) was classified as possibly related to organ preservation by the local investigator; all others were not related to the study solution. At the end of follow-up, 79.2% of adverse events (UW 81.8% vs. HTK 77.3%) had resolved without sequelae.

Six patients (UW 2 vs. HTK 4; P = 0.164) required re-operation, two of them for graft pancreatitis, two for bowel obstruction, for leakage of the intestinal anastomosis and one pancreatectomy after venous thrombosis.

Discussion

When compared with other solid organ transplants, pancreas transplantation is still burdened with significant rates of early graft loss [12–14]. Because of the high vulnerability of the pancreas, a meticulous surgical technique is essential to achieve a favorable early post-transplant outcome. A second major factor influencing post-transplant organ function is ischemia-reperfusion injury to the graft. Post-transplant pancreatitis remains one of the most significant nonimmunological complications after pancreas transplantation [15] and has been reported in up to 35% of pancreas transplantations [16]. Therefore, optimal organ preservation with efficient flushing and quick cooling of the organ with a protective solution might be of particular relevance in pancreas transplantation as compared with other abdominal organs. UW solution has been specifically developed for experimental pancreas transplantation [2], and has been the standard for organ perfusion in abdominal organ transplantation for the last 20 years. However, probably because of lower viscosity and lower costs, in the last decade HTK solution, originally designed as a cardioplegic solution, has been increasingly put into use for perfusion of abdominal organs. Both solutions profoundly differ by their mechanism of organ protection: UW solution contains osmotic-effective substances (lactobionate, raffinose, hydroxyethyl starch), is viscous and rich in potassium. HTK has a low viscosity, contains low quantities of potassium, and requires a larger volume for equilibration [17]. Experimental studies showed favorable outcomes of HTK preservation in a porcine pancreas autotransplant model [7] depending on the duration of cold ischemia [4]. Clinically, pancreas perfusion with HTK results in marked swelling of the organ [5,6,9], which has been attributed to the low viscosity together with the higher perfusion volume used. As the pancreas is considered a low volume organ [18], interstitial edema was deemed to translate into more pronounced organ damage. Only a few retrospective studies have addressed the validity of HTK perfusion in pancreas transplantation in comparison to UW-solution, including one follow-up report [5–10]. The largest series of HTK-perfused pancreas transplants was reported by Agarwal *et al.* [7] who retrospectively evaluated 78 patients and compared a historical control of 10 patients with UW-perfused pancreas transplants. They found similar results with both preservation solutions and reported an excellent 1-year graft survival of 93% for the HTK group. In our series, there was no statistically significant difference in graft survival between both the groups with a 6-month survival of 90.2% (UW) vs. 85.2% (HTK). Others also found comparable rates of pancreas graft survival using either perfusion solution [6,9,10]. Of note, in Agarwal's study, the authors reported lower levels of serum lipase and amylase on the first postoperative day as compared with our study, or of other investigators [6,9]. This might be in part attributable to the shorter mean cold ischemia time (9 ± 3 vs. 11 ± 4 h) in our cohort. Another interesting point is that the authors used

low amounts of HTK (3900 ml) for abdominal multi-organ perfusion. While many centers use the amount of 8000–12000 ml of HTK for *in situ* perfusion, as recommended by the company [6,9], the Indiana group even decreased their HTK perfusion volume compared with their previous report [8]. The clinical aspect of a marked swelling of the HTK-perfused organ during reperfusion intuitively evokes concerns about graft damage and centers using higher HTK volumes for perfusion also reported higher enzyme levels early post-transplantation [6,9,10]. The University of Michigan group [10] used approximately 5000 ml of HTK flush and in their retrospective series of 36 HTK and 41 UW patients; 90-day graft survival was 86.4% (HTK) vs. 87.5% (UW) for SPK patients with peak serum enzyme levels in the range of our findings. No obvious benefical effect of lower HTK flush volumes on postoperative graft function can be derived from these few studies, however the data indicate that further exploration of the effects of large HTK flush volumes on ischemia/reperfusion injury might be of interest in clinical pancreas transplantation.

Early graft loss in our study occurred in five patients (7.4%), with three (11.1%) cases in the HTK group and two (4.3%) in the UW group. This difference was not statistically significant and Agarwal *et al.* reported similar findings (6.41% graft loss) in their cohort of 78 HTK patients. In contrast, Becker reported somewhat higher rates of 90-day graft loss (HTK 14.6% vs. UW 17.0%) in their series of 95 patients; however none of the studies found a statistically significant difference between both preservation solutions. Englesbe *et al.* [10] further reported an overall 9% graft thrombosis rate with a significantly higher percentage of acute rejection episodes in the HTK group compared with UW-perfused organs (30.5% vs. 12.2%). Becker *et al.* [9] reported comparable rates of acute rejection for both HTK- and UW-perfused grafts in their cohort (27.1% vs. 27.7%). In our series, we experienced two cases of graft thrombosis, and a low rate of 2.9% of acute rejections. While one graft thrombosis was classified by the local investigator as possibly related to organ perfusion, numerous other factors like donor age, donor BMI, length of donor ICU stay and cause of death might also influence the occurrence of graft thrombosis, and it is hard to derive any conclusion from these two cases in our series. While in our, as well as in Becker's [9] study, immunosuppression was based on induction therapy using anti-thymocyte globulin, followed by a triple drug combination of tacrolimus, mycophenolate acid and steroids, a different regimen was used in the Englesbe study [10]. While in our, as well as the other published studies, no difference in short-term graft survival was found, we tried to further characterize the endocrine function of the pancreas grafts by monitoring the requirement for exogenous insulin and determining C-peptide levels. Following the protocol, postoperative blood glucose in the study population was strictly maintained at blood levels below 130 mg/dl for 3 weeks. This might explain the quite high number of patients receiving insulin on pod 1. Interestingly, more patients in the UW group required insulin postoperatively together with higher number of patients requiring insulin during the first 3 months after transplantation when compared with HTK group patients. However, the C-peptide levels revealed good endocrine function without any inter-group differences. Late functional evaluation of the blood glucose control (HbA1c and oral glucose tolerance testing) showed equally good function in both the groups during the first 6 months.

One major limitation of this study is the fact that we included only 27 patients in the HTK group versus 41 patients in the UW group. Early graft loss occurred in three HTK versus two UW patients and the limited number of patients included might have resulted in a type II statistical error. The discrepancy of patients in both the groups despite randomization is explained by the fact that this multicenter study was designed as a phase III trial for Germany and Belgium (phase IV for Austria) with the final goal to include 120 patients. However, following approval of HTK for abdominal organ perfusion and changing of graft allocation rules in Germany, the advisory committee decided to stop the study.

Another limitation is that not all patients underwent the same procedure, as three patients received a pancreas transplant alone (two PTA, one PAK). Further, three patients were lost to follow-up. Also, in this patient cohort, cold ischemia time of the pancreas graft was rather short with a mean of 10 h. Because of long distances between the procurement hospital and the transplant center, cold ischemia time is longer in many countries, and whether such longer ischemia times might produce statistically significant differences in outcome between both perfusion solutions (as suggested by data from kidney transplantation) [19], cannot be derived from this study.

In summary, this prospective, randomized study, in concordance with the findings of previous retrospective comparisons of pancreas perfusion with HTK versus UW solution, demonstrated equally good patient- and graft survival for both preservation fluids. HTK solution appears to be equally suitable as UW solution for *in situ* perfusion and organ preservation in clinical pancreas transplantation.

Authorship

MB: analyzed the data, wrote the paper and designed the figures. SS: designed and performed the study and

collected the data. WS, UJH, RT, JML, WS, and WM: performed the study and collected the data. RM and AK: designed and performed the study, critically revised and approved the manuscript.

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References

1. Belzer FO, Ploeg RJ, Knechtle SJ, *et al.* Clinical pancreas preservation and transplantation. *Transplant Proc* 1994; **26**: 550.
2. Wahlberg JA, Love R, Landegaard L, Southard JH. 72-Hour preservation of the canine pancreas. *Transplantation* 1987; **43**: 5.
3. Bretschneider HJ. Myocardial protection. *Thorac Cardiovasc Surg* 1980; **28**: 295.
4. Troisi R, Meester D, Van Den Broecke C, *et al.* Physiologic and metabolic results of pancreas cold storage with histidine-tryptophan-ketoglutarate-HTK solution (Custodiol) in the porcine autotransplantation model. *Transpl Int* 2000; **13**: 98.
5. Hesse UJ, Troisi R, Jacobs B, *et al.* Cold preservation of the porcine pancreas with histidine-tryptophan-ketoglutarate solution. *Transplantation* 1998; **66**: 1137.
6. Potdar S, Malek S, Eghtesad B, *et al.* Initial experience using histidine-tryptophane-ketoglutarate solution in clinical pancreas transplantation. *Clin Transplant* 2004; **18**: 661.
7. Agarwal A, Murdock P, Pescovitz MD, *et al.* Follow-up experience using histidine-tryptophane ketoglutarate solution in clinical pancreas transplantation. *Transplant Proc* 2005; **37**: 3523.
8. Fridell JA, Agarwal A, Milgrom ML, *et al.* Comparison of histidine-tryptophan-ketoglutarate solution and University of Wisconsin solution for organ preservation in clinical pancreas transplantation. *Transplatation* 2004; **77**: 1304.
9. Becker T, Ringe B, Nyibata M, *et al.* Pancreas transplantation with histidine-tryptophan-ketoglutarate (HTK) solution and University of Wisconsin (UW) solution: is there a difference? *J Pancreas* 2007; **8**: 304.
10. Englebe MJ, Moyer A, Kim DY, *et al.* Early pancreas transplant outcomes with histidine-tryptophan-ketoglutarate preservation: a multicenter study. *Transplantation* 2006; **82**: 136.
11. Konigsrainer A, Steurer W, Margreiter R. Multiple abdominal organ procurement for multiple recipients. Donor management and procurement. *Curr Opin Organ Transplant* 1999; **4**: 135.
12. Zhang R, Florman S, Devidoss S, *et al.* A comparison of long-term survivals of simutaneous pancreas-kidnea transplant between Afican American and Caucasian recipients with basiliximab induction therapy. *Am J Transplant* 2007; **7**: 1815.
13. Martins L, Pedroso S, Henriques AC, *et al.* Simultaneous pancreas-kindey transplantation: five-years results from a single center. *Transplant Proc* 2006; **38**: 1929.
14. Gruessner AC, Sutherland DE. Pancreas transplant outcomes for Unites States (US) and non-US cases as reported to the United Network for Organs Sharing (UNOS) and the International Pancreas Transplant Registry (IPTR) as of June 2004. *Clin Transpl* 2004; **19**: 433.
15. Maglione M, Hermann M, Hengster P, *et al.* A novel technique for heterotopic vascularized pancreas transplantation in mice to assess ischemia reperfusion injury in graft pancreatitis. *Surgery* 2007; **141**: 682.
16. Fernando-Cruz L, Sabater L, Gilabert R, *et al.* Native and graft pancreatitis following combined pancreas-renal transplantation. *Br J Surg* 1993; **80**: 1429.
17. De Boer J, De Meester J, Smits JM, *et al.* Eurotransplant randomized nulticenter kidney graft preservation study comparing HTK with UW and Euro-Collins. *Transpl Int* 1999; **12**: 447.
18. Kubo S, Yamamoto K, Magata Y, *et al.* Assessment of pancreatic blood flow with positron emmission tomography and oxygen- 15 water. *Ann Nucl Med* 1991; **5**: 133.
19. Roels L, Coosemans W, Donck J, *et al.* Inferior outcome of cadaveric kidneys preserved for more than 24 hr in histidine-tryptophan-ketoglutarate solution. Leuven Collaborative Group for Transplantation. *Transplantation* 1998; **66**: 1660.