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Comparison of Histidine-Tryptophan Ketoglutarate and University of Wisconsin Solutions as Primary Preservation in Renal Allografts Undergoing Pulsatile Perfusion

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ABSTRACT

Introduction. University of Wisconsin (UW) solution is the standard preservation solution for organ transplantation. Histidine-tryptophan ketogluatarate (HTK) solution has been used increasingly for kidney, pancreas, and liver transplantation. This study compared HTK and UW used during kidney procurement with subsequent pulsatile perfusion.

Methods. Between January and October 2003, 91 deceased renal and simultaneous kidney pancreas transplants were performed (UW, $n = 41$, and HTK, $n = 50$). There were no differences with regard to donor and recipient demographics or cold ischemia.

Results. Delayed graft function occurred in 3 (7%) of UW and 4 (8%) of HTK-preserved kidneys (P = NS). There were no significant differences between patient or graft survival. There was an anticipated difference between total preservative volumes used (HTK: 4.1 ± 1.0 vs UW: 3.0 ± 0.5; $P < .005$).

Conclusion. UW and HTK appear to have similar efficacy in kidney preservation with pulsatile perfusion. HTK preservation solution can be used safely in conjunction with pulsatile preservation for cold storage of renal allografts.

UNIVERSITY OF WISCONSIN solution (UW) is currently the standard preservation solution used for abdominal organ transplantation. Histidine-tryptophan ketogluatarate (HTK) solution, developed in the 1970s by Bretschneider as a cardioplegia solution,[1] is being used increasingly for kidney,[2] pancreas,[3] and liver transplantation.[4] The composition of these two solutions is described below (Table 1). UW contains metabolically inert substrates like lactobinate and raffinose, colloid carrier hydroxyethylstarch, and oxygen radical scavengers, glutathione, allopurinol, and adenosine. HTK contains less potassium and a strong histidine buffer that increases the osmotic effect of mannitol. Tryptophan serves as a membrane stabilizer and ketoglutarate as a metabolism substrate. Perhaps the most noticeable difference is the very low viscosity leading to the necessity of larger volumes in order to assure achievement of equilibrium.

European studies have compared the impact of these solutions in clinical kidney preservation, suggesting comparable delayed graft function (DGF) and allograft survival.[2,5] In addition, it has been suggested that the outcome is inferior of cadaveric kidneys preserved in HTK compared to UW solution with cold ischemia times greater than 24 hours.[6] Though the role of pulsatile perfusion in kidney preservation remains controversial, it has been shown to significantly reduce the rates of DGF in comparison to statically stored kidneys.[7] The benefits of pulsatile perfusion may be more pronounced with organs from marginal donors not only by reducing delayed graft function but by providing means to assess organ viability and function prior to transplantation.[8] Our center has a long history of placing all locally procured renal allografts on pulsatile perfusion. With the increasing use of HTK preservation of harvested organs, we felt it was important to determine whether it was safe to use pulsatile perfusion in conjunction with this solution.

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Table 1. Comparison of Constituents of UW vs HTK Solution

Component	UW (mmol/L)	HTK (mmol/L)
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

The aim of this retrospective, single-center study was to compare HTK and UW solution when used in conjunction with subsequent pulsatile perfusion with regard to initial graft function and survival in kidney transplantation.

MATERIALS AND METHODS

All kidneys were procured from cadaveric donors and were transplanted at Indiana University Medical Center. The kidneys were procured using an en bloc technique following aortic flush with either preservation solution. Imported extraregional kidneys were excluded from the analysis. The kidneys were separated and perfused individually at 4°C and at 60 beats per minute with 1 L of Belzer MPS perfusate (Transmed Corp, Elk River, Minn, USA; Table 2). It is important to note that Belzer MPS perfusate and UW are two distinct solutions. The Waters perfusion machine provides a fixed-pressure system that allows manipulation of the perfusion pressure as necessary. All kidneys were perfused at a systolic pressure below 40 mm Hg. Perfusion characteristics (renal flow, renal systolic blood pressure, and hypothermic perfusion time) were measured when the kidneys were initially placed on machine perfusion and every 30 minutes thereafter throughout the period of pulsatile perfusion.

Our program converted from UW solution to HTK solution for all abdominal organ procurements on May 1, 2003. In this study, we compared the final 41 kidney transplants performed using UW preservation fluid (mean follow-up 14.8 ± 1.0 months) to the first 50 kidney transplants performed using HTK solution (mean follow-up 10.3 ± 1.6 months). In terms of outcomes, our intention was to compare early renal graft function following preservation with either HTK or UW solution. To this end, we analyzed graft and patient survivals during the follow-up period and serial serum creatinine and creatinine clearance posttransplant. In addition, a subset analysis was performed to determine whether there were any differences between the two groups when ischemia time was greater than 24 hours. These parameters were compared using the chi-square and Student t test. P value $\leq .05$ was considered significant.

Table 2. Constituents of Belzer MPS Solution

Sodium gluconate	80 mmol/L
Potassium phosphate, monobasic NF	25 mmol/L
Magnesium gluconate, USP (dihydrate)	5 mmol/L
Glucose, beta D (+)	10 mmol/L
Adenine (free base)	5 mmol/L
Ribose (D−)	5 mmol/L
HEPES (free acid)	10 mmol/L
Glutathione (reduced form)	3 mmol/L
Calcium chloride, USP (dihydrate)	0.5 mmol/L
Mannitol, USP	30 mmol/L
Modified hydroxyethyl starch	5.46 g/L
Sodium hydroxide	5 N

RESULTS

Between January and October 2003, 55 donors (HTK: n = 30, UW: n = 25) were included in the study. This resulted in 91 primary renal or simultaneous kidney pancreas transplantation. Donor and recipient demographics are summarized in Tables 3 and 4, respectively. There was no significant difference in donor organ perfusion systolic pressure (HTK: 36 ± 5 mm Hg vs UW: 38 ± 9 mm Hg; P = .26) or renal flow (HTK: 110 ± 22 mL/h vs 116 ± 35 mL/h; P = .38). The only significant difference between the organ donors in the two groups was the greater volume of solution used in the HTK group (HTK: 4.1 ± 1.1 L vs UW: 3.0 ± 0.5 L; $P < .05$). This is an expected difference as HTK is a less viscous solution and therefore requires this increased volume. Patient and graft survivals at the completion of the follow-up period were 98% for both groups. There was one death in each study group secondary to cardiac event (UW) and graft-versus-host disease (HTK). There was no graft loss secondary to acute rejection or technical complications. There was no difference in the rates of DGF, defined as the requirement for hemodialysis at least once during the first postoperative week (UW 7% vs HTK 8%). Creatinine clearance rates (Fig 1) and serum creatinine (Fig 2) were similar at all time points.

Nine (22%) patients from UW group and 12 (24%) from HTK group had total ischemia time greater than 24 hours (UW 25 ± 2 h vs HTK 25 ± 4 h). One patient from the

Table 3. Donor Demographics

	UW	HTK	P value
Age	38 ± 13	34 ± 16	NS
Gender			
Male	15	19	NS
Female	12	13	
Ethnicity			
Caucasian	23	27	NS
African-American	4	5	
BMI (kg/m^2)	25 ± 5	27 ± 8	.52
Cause of death			
Trauma	11	16	
CVA	15	14	
Anoxia	1	2	
Pressors			
Yes	6	7	NS
No	21	25	
Last serum creatinine (mg/dL)	1.3 ± 0.5	1.1 ± 0.4	.1
Volume of solution (L)	3.0 ± 0.5	4.1 ± 1.1	<.005
Pump systolic BP (mm Hg)	38 ± 9	36 ± 5	.26
Pump renal flow (mL/h)	116 ± 35	110 ± 22	.38

BMI, body mass index; CVA, cerebrovascular accident; BP, blood pressure.