Comparison of Histidine-Tryptophan Ketoglutarate Solution and University of Wisconsin Solution in Prolonged Cold Preservation of Kidney Allografts

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Although University of Wisconsin (UW) solution is the standard preservation solution for organ transplantation, Histidine-Tryptophan Ketogluatarate (HTK) solution has been increasingly used. This study compared HTK or UW for cold static storage of kidney allografts. In all, 149 renal transplants were performed with cold ischemic times (CI) greater than 16 hr (UW 87, HTK 62) and a subset analysis was performed with CI over 24 hr (HTK 31, UW 38). Data from receiving renal transplant centers focused on delayed graft function (DGF), patient and allograft survival. In CI greater than 16 hr, graft and patient survival were comparable. HTK cohort had lower DGF. In CI greater than 24 hr, there was no difference in patient survival, a trend towards improved graft survival in HTK, and decreased rate of DGF in HTK. This data suggests that UW and HTK have at least similar efficacy in kidney preservation at longer ischemic times.

Keywords: Kidney transplantation, Organ preservation solution, Organ procurement, Histidine-Tryptophan Ketogluatarate (HTK) solution, University of Wisconsin (UW) solution.

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University of Wisconsin solution (UW) is 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*, *3*), pancreas (*4*, *5*), and liver transplantation (*6*). UW contains metabolically inert substrates like lactobinate and raffinose, colloid carrier hydroxyethyl starch, and adenosine as an energy substrate. HTK contains less potassium and a strong histidine buffer that increases the osmotic effect of mannitol. Perhaps the most noticeable difference is the very low viscosity leading to the necessity of larger infusion 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 and allograft survival (*2*, *7*). In addition, it has been suggested that there is inferior outcome of deceased donor kidneys preserved in HTK compared to UW solution with cold ischemia (CI) times greater than 24 hr (*8*). We have previously reported our experience with renal allografts initially flushed with HTK or UW and subsequently preserved on a pulsatile perfusion apparatus and found no difference between the two solutions. The aim of this study was to evaluate HTK or UW solution when used for cold preservation of kidney allografts with extended cold preservation times with primary endpoints, including initial graft function and overall allograft survival.

MATERIALS AND METHODS

This study was a single center initiated analysis based on the responses to a survey from numerous renal transplant centers. All organs were procured by Indiana Organ Procurement Organization from deceased donors and were transplanted at various centers. These tissues and corresponding medical information were obtained after appropriate informed consent was obtained. The kidneys were procured using an en-bloc technique following aortic flush with either preservation solution. Our program converted from UW solution to HTK solution for all abdominal organ procurements on May 1, 2003. Only allografts which had CI greater than 16 hr were included in this analysis. A subset analysis involving CI over 24 hr was also performed. The UW preservation fluid cohort consisted of 87 allografts (mean follow-up 878±331 days) and 62 were preserved with HTK solution (mean follow-up 510±215 days). Our intention was to compare early renal graft function following preservation with either HTK or UW solution. Therefore, the incidence of primary nonfunction (PNF) and delayed graft function (DGF) were the primary endpoints. PNF was defined as immediate anuria in absence of surgical etiologies of allograft failure. DGF was restricted to the need for dialysis within the first postoperative week. Graft and patient survival were assessed during the follow-up period, and serial serum creatinine and blood urea nitrogen (BUN) posttransplant were followed. These univariate parameters were compared using the Chi Squared and Student's *t* test. Logistic regression using a multivariate setting was implemented to derive a probabilistic model for the incidence of DGF. Patient and graft survival was analyzed using the Kaplan Meier method. *P* value ≤ 0.05 was considered significant.

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RESULTS

Between January 2002 and November 2004, 131 donors (HTK: n=51, UW: n=80) were included in the study. This resulted in 149 primary renal transplantations (HTK: n=62, UW: n=87) in which CI was greater than 16 hr (113 renal allografts were excluded). A subset analysis was performed on those allografts with CI over 24 hr (HTK: 31 allografts; UW: 38 allografts). Donor and recipient demographics are summarized in Tables 1 and 2, respectively.

In CI greater than 16 hr, there was no difference in donor (Table 1) or patient (Table 2) demographics except for cold (HTK: 25.7±7.3 vs. UW: 22±7.6 hr; P=0.003) and warm ischemic times (HTK: 35±15 vs. UW: 28±11 min; P=0.004). Both graft (HTK: 92% vs. UW: 84%; P=0.24) and patient survival (HTK: 95% vs. UW: 94%; P=0.59) were comparable. HTK had lower rates of DGF (HTK: 24% vs. UW: 56%; P=0.004). The HTK cohort also had a higher patient quality of life as measured by Karnofsky Performance Status Scale (KPS) (HTK: 85±8 vs. UW: 80±17; P=0.03). The multivariate analysis revealed three covariates predictive of DGF (odds ratio): UW solution (4.1; P=0.003), cold ischemic time (1.06; P=0.03), and anti-human lymphocyte antibody (1.03; P=0.005)

The subset analysis involved CI greater than 24 hr with 31 allografts from the HTK and 38 from the UW cohort. The patient demographics revealed no significant difference between the two groups (Table 3) except for increased warm ischemic times in HTK (HTK: 38±18 vs. UW: 29±9 min; P=0.03). There was no difference in patient survival (HTK: 100% vs. UW: 95%; P=0.68). There was a trend toward improved graft survival in the HTK cohort (HTK: 97% vs. UW: 82%; P=0.1). This could be explained by the decreased rate of DGF in the HTK cohort (HTK: 16% vs. UW: 56%; P=0.005). The only significant variable in the multivariate analysis was the preservation solution. UW had a greater tendency toward DGF than HTK (odds ratio: 3.8; P=0.028).

DISCUSSION

Proper organ preservation is critical for long-term allograft function in kidney transplantation. Effective organ preservation techniques should minimize delayed graft function rates and primary nonfunction rates. Delayed graft function is a significant burden to the transplant community. It is associated with higher rates of long term allograft failure (*9*) and is quite difficult financially (*10*) and medically to manage. Immediate graft function should result in more favorable long-term graft survival. In addition, given the growing scarcity of renal allografts, it is critical that optimal kidney preservation is implemented to assure efficient utilization of this limited resource.

HTK solution is being used with increasing frequency as a preservation solution for abdominal transplantation. Experiences in renal transplantation have found HTK and UW to be essentially equivalent preservation solutions (*2*) with a clear advantage of both solutions over Euro-Collins solution (*11*). In the most recent update of the European randomized

TABLE 1. Donor demographics (cold ischemia time >16 hours)

Category	HTK	UW	*P* value
Donors	51	80	
Allografts	62	87	
Flush volume	3.4±1.3	2.7±0.9	0.0005
UNOS expanded criteria	8	4	0.37
Age (years)	33±19	31±14	0.33
Male/female	32/19	59/21	0.78
Cause of death			
Medical	24	29	0.82
Trauma	27	51	0.83
Peak creatinine	1.3±0.5	1.3±0.4	0.88
Terminal creatinine	1.0±0.4	1.0±0.4	0.56
Peak blood urea nitrogen	17±7	17±8	0.89
Terminal blood urea nitrogen	12±7	13±7	0.49

TABLE 2. Recipient demographics (cold ischemia time >16 hours)

Category	HTK	UW	*P* value
N	62	87	
Age (years)	50±14	46±16	0.13
Male/female	38/24	53/34	0.82
Primary nonfunction	2 (3.2%)	5 (5.7)	0.97
Delayed graft function	15 (24.1%)	49 (56.1%)	0.004
Acute rejection	1 (1.6%)	7 (8%)	0.56
Ethnicity			
White	42	69	0.86
African American	16	15	
Hispanic	3	2	
Other	1	1	
Disease			
HTN	14	15	0.95
Diabetes mellitus	18	21	0.97
GN	11	9	0.78
Other	17	36	0.58
ABDR mismatch	2.7±1.7	2.6±1.6	0.95
PRA>30%	7 (11.3%)	13 (14.9%)	0.98
Pretransplant dialysis	56 (90%)	80 (92%)	0.99
Cold ischemic time (hours)	25.7±7.3	22±7.6	0.003
Warm ischemic time (minutes)	35±15	28±11	0.004

TABLE 3. Recipient demographics (cold ischemia time >24 hours)

Category	HTK	UW	*P* value
n	31	38	
Patient survival	100%	95%	
Graft survival	97%	82%	
Recent crea	1.35 (0.56)	1.29 (0.34)	NS
Age (years)	48 (13)	48 (17)	NS
Male/female	21/10	27/11	
Panel reactive antibodies	11 (20)	14 (27)	NS
Cold ischemia (hours)	31 (6)	29 (6)	0.13
Warm ischemia (minutes)	38 (18)	29 (9)	0.01
Primary nonfunction	3%	6%	NS
Delayed graft function	16%	56%	<0.05
Karnofsky Performance Status Scale post	84 (8)	78 (18)	0.11

multicenter trial, UW and HTK had comparable delayed graft function rates, declining serum creatinine, and rising creatinine clearances. We have previously reported our recent experience with renal allograft preservation with HTK combined with pulsatile perfusion utilizing modified UW solution in which there was comparable immediate renal function (*3*) In this report, a cost analysis was performed which showed that HTK was financially comparable to UW despite the larger flush volumes necessary.

However, there has been concern for the efficacy of HTK in renal allograft preservation with increased CI. Roels et al. (*8*) reported that there were clinically significant differences between UW and HTK for simple cold storage times greater than 24 hr. The difference in delayed graft function rates between UW (23.9%) compared to HTK kidneys (50%) was significant. This report was the impetus to evaluate our experience with HTK.

There are many differences between this report and the previously mentioned analysis by Roels et al. which prevent direct comparisons of the data; perhaps the most limiting factor is the definitions of delayed graft function. In the study by Roels et al., delayed graft function was limited to the need for hemodialysis within the first week posttransplant or oliguria (less than 0.5 L in 24 hr). The authors of this report applied a more stringent criterion involving the need of hemodialysis within the first week postoperatively. This alone could explain the discrepancies in the results of both studies. Despite this, in our analysis there appears to be equal efficacy in the preservation of renal allografts with HTK for longer than 24 hr compared to with UW as previously suggested by that study.

The ideal study which could clearly identify significant differences in cold preservation of renal allografts between UW and HTK should be a randomized blind study with properly powered sample sizes. Therefore, definitive conclusions about the efficacy of either solution from this retrospective analysis should be limited and conservative at best. There was no significant change in allocation criteria or system during the study period and therefore it is difficult to account for the differences in cold ischemia times. This study involved kidney allografts that were sent to numerous transplant centers which may individually have experienced institutional differences in surgical technique and operating room practices. The centers in which the data was collected were not case-control matched. The limitations of this retrospective study prevent clear explanations for the differences in cold and warm ischemia. There is sufficient evidence in this report to suggest that preservation of renal allografts with prolonged cold ischemia times have noninferior outcomes compared to UW.

CONCLUSION

To date, HTK solution is at least comparable to UW for cold preservation of renal allografts. We report that with prolonged cold ischemia times (greater than 24 hr), HTK is not inferior to UW solution as previously suggested by other authors and may in fact provide better protection for the prevention of delayed graft function compared to UW solution.

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