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J. de Boer
J. De Meester
J. M. A. Smits
A. F. Groenewoud
A. Bok
O. van der Velde
I. I. N. Doxiadis
G. G. Persijn

Eurotransplant randomized multicenter kidney graft preservation study comparing HTK with UW and Euro-Collins

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J. de Boer (✉) · J. De Meester · J. M. A. Smits · A. Bok · O. van der Velde · G. G. Persijn
Eurotransplant International Foundation, P. O. Box 2304, 2301 CH Leiden, The Netherlands
e-mail: jdeboer@eurotransplant.nl
Fax: + 31-71-5790057

A. F. Groenewoud
Department of General and Transplantation Surgery, Klinikum Rechts der Isar der Technischen Universität, Ismaniger Strasse 22, 81675 München, Germany

I. I. N. Doxiadis
Eurotransplant Reference Laboratory, Department of Immunohaematology and Blood Bank, Leiden University Medical Center, P. O. Box 9600, 2300 RC Leiden, The Netherlands

Abstract The aim was to evaluate the effect of HTK compared to UW and Euro-Collins (EC) on the initial graft function and long term graft survival in two prospective randomized studies. Only kidneys from heart-beating, kidney-only or kidney + heart donors were eligible for entry. Initial non-function (INF) was defined as the absence of life-sustaining renal function, requiring dialysis treatment on two or more occasions, during the first week after transplantation. To evaluate the contribution of the preservation solutions on INF in relation to other factors, a multivariate, 2-step logistic regression model was used. Randomization was performed between July 1990 and September 1992. The UW-HTK study comprised 342 donors and 611 transplants (UW: 168 donors and 297 transplants, HTK: 174 donors and 314 transplants). In the EC-HTK study 317 donors and 569 transplants were included (EC: 155 donors and 277 transplants, HTK: 162 donors and 292 transplants). INF occurred in 33% of either HTK-(n = 105) or UW-(n = 99) preserved kidneys (P = NS), and in 29% of the HTK-(n = 85) and in 43% of the EC-(n = 119) preserved kidneys (P = 0.001). Multivariate analysis showed no significant influence of the preservation solution on the incidence of INF in the UW-HTK study, but factors contributing to INF were donor age, cause of death, retransplantation, and cold ischemic period. The EC-HTK study showed a significantly higher risk of INF, using EC as preservation, in addition to cold ischemic period and donor quality. The 3-year graft survival of HTK-preserved kidneys was 73%, compared to 68% for UW-preserved kidneys in the UW-HTK study (P = NS); while the 3-year graft survival of HTK preserved kidneys was 70% compared to 67% for EC-preserved kidneys in the EC-HTK study (P = NS). We can conclude that HTK is comparable to UW in its preservative abilities, using kidneys from heart-beating kidney-only donors, whereas EC as renal preservation solution should be avoided.

Key words Kidney transplantation · Initial non-function · Graft survival · UW · Euro-Collins · HTK

Introduction

Preservation solutions are used to maintain the organ in optimal condition from the time of explantation until transplantation. Organ flush with a cold solution and subsequent storage at a low temperature is an efficient and simple method [2, 3, 5]. In 1977, the phosphate-buffered Eurocollins (EC) solution was introduced as the standard solution for kidney graft preservation in the Eurotransplant organization [15]. As of 1986, the Uni-

Table 1 Components of the preservation solutions

Substance	HTK solution[1]	UW solution[2]	EC solution[3]
Sodium	15	30	10
Potassium	10	130	115
Magnesium	4	5	–
Buffer	180 Histidine 18 Histidine HCL	5 $H_2PO_4^-$ 20 HPO_4^-	15 $H_2PO_4^-$ 42 HPO_4^- 10 HCO_3^-
Others	30 Mannitol 1 α-Ketoglutarat 2 Tryptophan	50 g/l Haes 30 Raffinose 5 SO_4^- 100 Lactobionate 5 Adenosine 3 Gluthatione 1 Allopurinol	194 Glucose
Osmolarity	310 mOsm/l	320 mOsm/l	355 mOsm/l

Components are expressed as mmol/L unless otherwise indicated
[1] Produced and distributed by Dr. F. Köhler Chemie GmbH, Alsbach-Hähnlein, Germany
[2] Manufactured by NPBI in the Netherlands and supplied by E.I. Du Pont de Nemours Inc, Wilmington, Delaware, USA
[3] Either purchased from Fresenius AG, Oberursel, Germany or prepared by the hospital pharmacist, according to the required formulation

versity of Wisconsin (UW) preservation solution gradually replaced EC as the preservation fluid of choice for abdominal organs obtained from multi-organ donors [1, 13, 14]. Meanwhile, some centers also used, for kidney-only preservation, the Bretschneider-HTK solution, which was originally designed for cardioplegia in open heart-surgery, but proved also to be a potentially good organ preservation solution in experimental studies [8, 9, 10]. Table 1 summarizes the main differences in the composition of the preservation solutions. In this paper we present the results of two randomized clinical multicenter studies, comparing the HTK preservation solution with both the UW- and the EC solution, with regard to the initial function and long term graft survival in cadaveric renal transplantation.

Materials and methods

Study design

The Eurotransplant[1] donor centers could participate in only one of the studies. A randomization scheme enabled equal distribution of the preservation solutions per donor-center in each of the studies. For both studies, the randomized assignment of the preservation solution for donors was performed by the duty office of the Eurotransplant International Foundation.

[1] Eurotransplant is an organ exchange organization, in which transplantation centers and tissue typing laboratories from Austria, Belgium, Germany, Luxembourg and the Netherlands are collaborating since 1969.

Inclusion criteria for donors and recipients

As earlier publications have demonstrated a superior graft outcome of liver and pancreas preserved with UW as compared to EC, randomization of donors in cases of abdominal multi-organ donation was considered ethically not justifiable. Hence, in the present studies, only kidneys from cadaveric, heart-beating, kidney-only, or kidney + heart donors were included. Exclusively kidney-only transplant candidates were eligible for the studies.

Preservation and surgical procedures

The usual technique for organ retrieval and preservation was applied [18]. The recommended volume for the in-situ flush-out through the cannulated aorta was 5000–6000 ml for HTK, 1000–2000 ml for UW, and 4000 ml for EC. After explantation, the renal allografts were packed and stored on non-sterile melting ice in standard organ transport boxes.

Recipient selection

Recipient selection was based on ABO blood group compatibility, HLA-A,B,DR mismatching, HLA immunization and waiting time, using the Eurotransplant computer selection program.

End points

The incidence of initial non-function (INF) per solution, as well as the long-term effect of INF on the transplantation results, were analyzed. INF was defined as the absence of life-sustaining renal function requiring dialysis treatment on two or more occasions during the first week after transplantation. This definition of INF included kidneys recovering after dialysis treatments, as well as permanent non-functioning grafts.

Table 2 Study population

	UW-HTK study		EC-HTK study	
	UW	HTK	EC	HTK
No. donors randomized	172	177	180	182
No. kidneys discarded	13	10	18	10
Tp outside Eurotransplant	6	1	5	6
Insufficient follow-up	13	13	6	40
Kidneys failed ≤ 48 hours	15	18	15	13
– Hyperacute rejection	5	7	6	3
– Non viable organ	5	4	2	3
– Vascular complications	7	5	1	7
– Other	1	2	6	0
Study population for analysis				
No. of donors	168	174	155	162
No. of transplants	297	314	277	272
Long term follow-up available	281	291	254	253

Statistical analyses

For each study demographic data of the donors, recipients, and transplants were compared with the two preservation solutions to confirm the adequacy of randomization for the donors, and to check for any relevant differences in characteristics between the recipient populations. The chi-square test was applied for discrete variables, while the Mann-Whitney test was used for continuous variables.

The incidence of INF was analyzed univariately, as well as by a multivariate 2-step logistic regression model. In the first step, the following factors were entered: donor age, cause of death, donor quality [defined as poor when, during the last 24 h before nephrectomy, there had been either a cardiac arrest, episodes of severe hypotension (i.e. systolic blood pressure < 80 mm Hg), oliguria (urine output less than 400 ml/24 h) or a serum creatinine level > 2 mg/dl], number of HLA DR mismatches, peak percentage of panel reactive antibodies (PRA), recipient age, number of previous transplants of the recipient, and cold ischemic period. In the second step the effect of the preservation solutions on INF was tested. For each of the two studies a separate model was built.

Graft survival probabilities at 3 years were calculated by the Kaplan-Meier method. The significance of the differences between groups of patients was tested by a log rank test [12]. Transplantation was considered successful if the recipient remained alive without re-institution of permanent dialysis. Deaths with a functioning graft were considered as graft failures.

Table 3 Relative risks for delayed graft function per variable

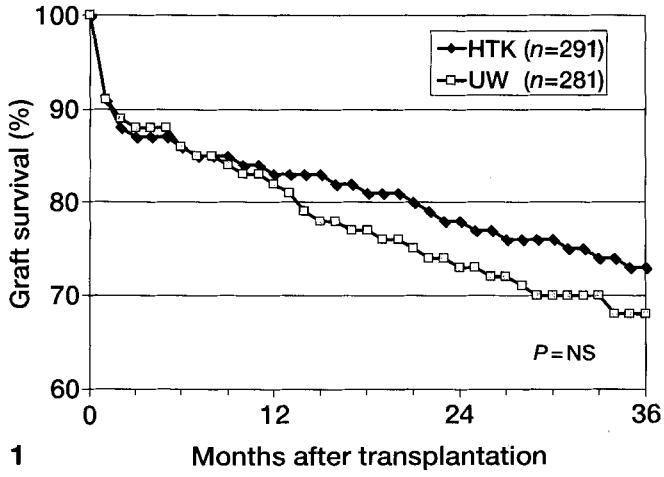
Variable	UW-HTK study		EC-HTK study	
	RR	*P*-value	RR	*P*-value
Solution:				
HTK	1.000	0.64		
UW	0.918			
HTK			1.000	0.003
EC			1.427	
Donor quality:				
poor	1.000	0.44	1.000	0.05
good	1.157		1.525	
Donor age:				
≤ 30 yrs	1.205	0.02	1.143	0.59
31–45 yrs	1.000		1.000	
46–55 yrs	1.662		1.347	
> 55 yrs	2.219		1.126	
Donor cause of death:				
trauma capitis	1.000	0.04	1.000	0.18
multi-trauma	0.881		2.037	
cerebro vascular accident	1.364		1.691	
other	2.095		1.624	
Cold ischemic period:				
≤ 18 hrs	1.000	0.01	1.000	0.0004
19–24 hrs	0.771		1.303	
25–35 hrs	1.456		1.626	
> 35 hrs	1.634		5.960	
Recipient age:				
≤ 30 yrs	0.656	0.08	1.070	0.76
31–45 yrs	1.000		1.000	
46–55 yrs	1.228		0.817	
> 55 yrs	1.410		1.022	
Previous transplant(s):				
none	1.000	0.0001	1.000	0.10
one or more	3.311		1.434	
HLA-DR mismatches:				
0 mm	1.000	0.90	1.000	0.16
1–2 mm	0.977		0.803	
Peak PRA:				
0–5 %	1.000	0.38	1.000	0.78
≥ 6 %	0.798		1.080	
Coefficient of constant	–2.625		–2.803	

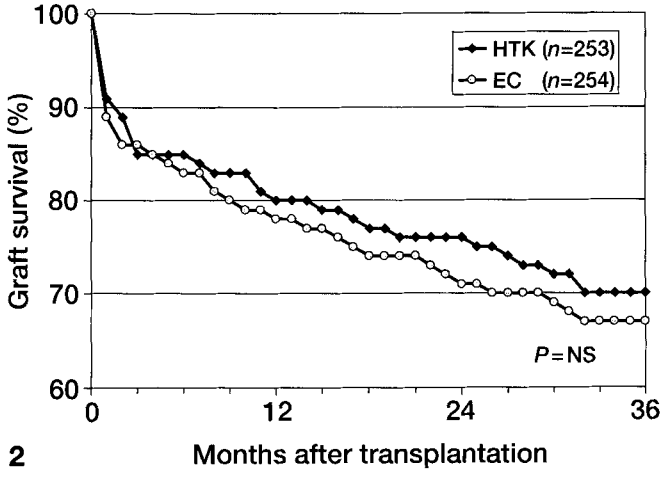
Results

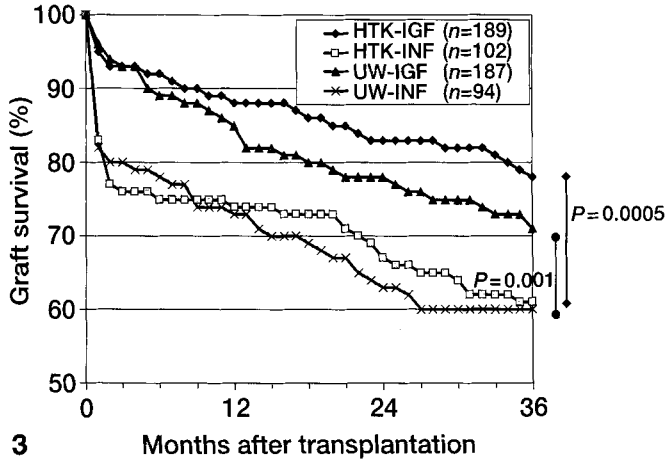
A consecutive series of eligible kidney donors ($n = 711$) was randomized from July, 1990 through September, 1992. Kidney grafts assessed as unsuitable for transplantation during the organ procurement, transplants performed outside the Eurotransplant area, and those with insufficient data were excluded from the study (Table 2). Sixty-one transplants failed within 48 hours post transplantation (Table 2). It was assumed that preservation solution played a minor role in these cases (i.e. positive HLA cross-match leading to hyperacute rejection, technical problems with arterial or venous anastomosis, etc). Therefore these transplants were excluded from the analysis.

No significant differences in donor age, donor cause of death, donor quality, number of HLA DR mismatches, peak percentage of panel reactive antibodies (PRA), recipient age, number of previous transplants of the recipient, and cold ischemic period could be found between the two groups in either of the two studies.

In the UW-HTK study, 33 % (105/314) of the recipients in the HTK-group had INF of the transplanted kidney as compared to 33 % (99/297) in the UW group (P = NS). A significant difference was observed in the







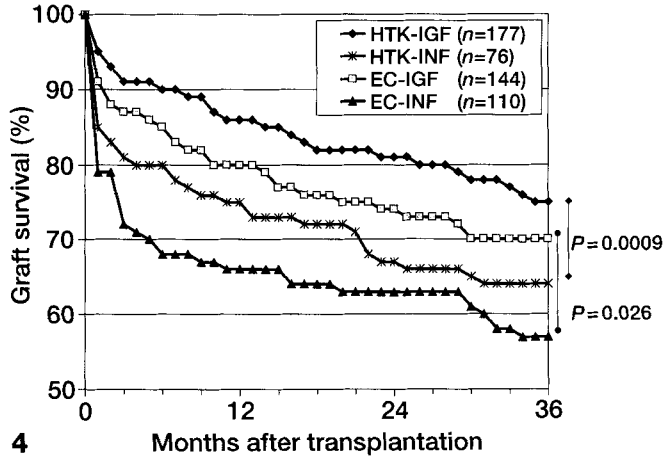


Fig. 1 3-years graft survival in the UW-HTK study

Fig. 2 3-years graft survival in the EC-HTK study

Fig. 3 Effect of initial graft function on graft survival in the UW-HTK study

Fig. 4 Effect of initial graft function on graft survival in the EC-HTK study

EC-HTK study. In the HTK group 29% (85/292) of the recipients had INF compared to 43% (119/277) in the EC group ($P = 0.001$).

The multivariate analysis in the UW-HTK study showed that the kind of preservation solution used was not associated with INF. But four other factors were indeed associated with INF: donor age, donor cause of death, retransplantation, and cold ischemic period (Table 3). In the EC-HTK study, the use of EC as preservation solution was seen to be associated with a higher incidence of INF. In this study, two other factors were also of prognostic value: donor quality and cold ischemic period (Table 3).

In the UW-HTK study, the overall graft survival at 1, 2 and 3 years after transplantation for the HTK-preserved kidneys was 83%, 77%, and 73% respectively, as compared with 81%, 73%, and 68% respectively for the UW preserved kidneys (figure 1, at 3 years: P = NS). In the EC-HTK study, the overall graft survival at 1, 2 and 3 years after transplantation for the HTK-preserved kidneys was 80%, 76%, and 70% respectively, as compared with 78%, 71%, and 67% respectively for the EC preserved kidneys (figure 2, at 3 years: P = NS).

For all preservation solutions in the 2 studies, long-term kidney graft survival was significantly better in cases of initial graft function (IGF) than that of patients with INF. In the UW-HTK study, HTK-preserved kidneys with IGF had a graft survival 1, 2 and 3 years of 88%, 83%, and 78%, versus 74%, 67%, and 61% respectively for HTK-preserved kidneys with INF (figure 3, $P = 0.0005$). Also UW-preserved kidneys with IGF had a better graft survival at 1, 2 and 3 years of 86%, 78%, and 71%, compared to 74%, 64%, and 60% respectively for the UW preserved kidneys with INF (figure 3, $P = 0.001$).

In the EC-HTK study, HTK-preserved kidneys with IGF had a graft survival at 1, 2 and 3 years of 86%, 81%, and 75%, versus 75%, 67%, and 64% respectively for HTK preserved kidneys with INF (figure 4, $P = 0.0009$). Also, EC preserved kidneys with IGF had a better graft survival at 1, 2 and 3 years of 75%, 67%, and 64%, compared to 66%, 63%, and 57% respectively for the EC-preserved kidneys with INF (figure 4, $P = 0.026$).

Discussion

The two multicenter studies demonstrate that, with regard to the potential of optimal preservation of cadaveric donor kidneys for transplantation, the UW and HTK solutions are equal, and that EC is clearly inferior to HTK with respect to the incidence of INF. The renal allografts procured from heart-beating, kidney-only and kidney + heart donors showed an incidence of INF during the first week after transplantation, of 33% for UW, of 33% and 29% for HTK, and of 43% for EC. The 3-year graft outcome showed no significant differences between the preservation solutions in either studies, although initially there was a higher incidence of graft loss in the EC- as compared to the HTK-group.

Many factors have been identified as contributing to initial non function. In order to evaluate the effect of the preservation solution, a multi-variate analysis was performed. With exception of the cold ischemic period, the independent factors were not identical in either studies. The EC preservation solution was also responsible for a higher incidence of INF in the EC-HTK study, confirming our univariate analysis. In the UW-HTK study, the more common risk factors (donor age, donor cause of death and re-transplantation) appeared to be of prognostic value, and no independent effect of the type of preservation solution was found.

These results indicate, that with respect to the current donor pool for kidney-only donation, intervention towards reduction of the incidence of initial non-function can only concentrate on limiting the cold ischemic period, besides avoiding the use of EC. This conclusion supports another approach of kidney allocation, in which the potential transplant candidates are already selected prior to the kidney explantation procedure. This is certainly feasible if the donor HLA typing is done on peripheral blood cells instead of spleen cells.

The incidence of INF for UW surpassed the results of an other trial carried out in the Eurotransplant area just prior to the start of our study [14]. A plausible explanation is, that during our study period, multi-organ donation led to the exclusion of several donors who were kidney-only donors in the Ploeg study. Our group has shown that the kidneys procured in the setting of a multi-organ procedure have a better outcome in comparison with kidneys procured from kidney-only donors [17].

Remarkable is the higher incidence of INF in the EC-HTK study in the case of a good quality, kidney-only donor, as compared to the poor quality donor. Possibly, poor quality donors were monitored better following the hypotensive period or the cardiac arrest. The corresponding better donor management perhaps reversed or prevented further ischemic injury [7, 11, 19].

Our study confirmed the common perception that kidney grafts suffering from INF have a poorer long-term outcome. This effect was observed for all preservation solutions. Therefore one could conclude that preservation solutions only have an immediate effect, but do not affect the long-term outcome. This should be taken into account in further preservation trials.

Previous analyses at the Eurotransplant database [4] and at a single center [16] both demonstrated a deleterious effect of HTK, in contrast to UW, on the 1-year graft outcome, if the cold ischemic period exceeded 24 h. In the current (controlled) UW-HTK study, this observation could neither be confirmed with respect to the incidence of INF, nor with respect to 1-year graft outcome.

Can our results in kidney-only donation be extrapolated to multi-organ donation?

In contrast to UW, multicenter studies assessing the effectiveness of HTK as liver- and/or pancreas preservation solution are currently not available. Single-center studies in liver transplantation suggest comparable results between UW and HTK [6].

The limited experience with HTK in kidney + pancreas transplantation is not sufficient to yield a reliable analysis. The promising results in kidney- and liver transplantation with the preservation solution Celsior®, like HTK, a cardioplegic solution, and with a similar composition (personal communication, D. Alfani), are interesting. This might indirectly support the usage of HTK in abdominal multi-organ procurement.

In conclusion, HTK is comparable to UW in its preservative abilities in cadaveric renal transplantation, using kidneys procured from heart-beating kidney-only donors, whereas EC, as renal preservation solution, should be avoided altogether. Unfortunately, other factors, in particular the cold ischemic period, still remain of crucial importance for the initial (non-)function of the renal graft, but might be addressed appropriately.

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Austria	Participation[2]
Medizinische Universitätsklinik, Graz	T
Chirurgische Universitätsklinik, Innsbruck	B
Krankenhaus der Elisabethinen, Linz	T
Allgemeines Krankenhaus, Linz	T
Universitätsklinik für Chirurgie, Wien	B
Belgium	
Universitair Ziekenhuis Antwerpen, Edegem	B
Academisch Ziekenhuis der Vrije Universiteit, Brussel	B
Hôpital Erasme, Bruxelles	B
Cliniques Universitaires St. Luc, Bruxelles	B
Universitair Ziekenhuis, Gent	T
Universitair Ziekenhuis Gasthuisberg, Leuven	T
Centre Hospitalier Universitaire, Liège	T
Germany	
Klinikum der Rheinisch-Westfälischen Technischen Hochschule, Aachen	T
Universitätsklinikum Benjamin Franklin, Berlin	B
Krankenhaus im Friedrichshain, Berlin	B
Kliniken der Freien Hansestadt, Bremen	B
Medizinische Einrichtungen der Heinrich-Heine-Universität, Düsseldorf	B
Klinikum der Universität, Essen	B
Klinikum der Johann-Wolfgang-Goethe-Universität, Frankfurt	B
Klinikum der Albert-Ludwigs-Universität, Freiburg	B
Klinikum der Georg-August-Universität, Göttingen	B
Klinikum der Martin-Luther-Universität, Halle	T
Klinikum der Ruprecht-Karls-Universität, Heidelberg	B
Universitäts-Krankenhaus Eppendorf, Hamburg	T
Nephrologisches Zentrum Niedersachsen, Hann. Münden	T
Klinikum der Medizinischen Hochschule, Hannover	B
Klinikum der Universität des Saarlandes, Homburg/Saar	T
Klinikum der Friedrich-Schiller-Universität, Jena	T
Klinikum Christian-Albrechts-Universität, Kiel	B
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Städtische Krankenanstalten Köln-Merheim, Köln	B
III. Medizinische Klinik, Kaiserslautern	B
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Klinikum der Stadt, Mannheim	T
Klinikum Rechts der Isar der Technischen Universität, München	B
Klinikum Großhadern der Ludwig-Maximilians-Universität, München	B
Klinikum Lahnberge der Philipps-Universität, Marburg	B
Klinikum der Johannes-Gutenberg-Universität, Mainz	B
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Academisch Ziekenhuis St-Radboud, Nijmegen	B
Academisch Ziekenhuis Dijkzigt, Rotterdam	T
Academisch Ziekenhuis, Utrecht	T

[2] T = Transplant center; B = Donor & Transplant center

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