Comparison of Pulsatile Perfusion and Cold Storage for Paired Kidney Allografts

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Use of pulsatile perfusion to optimize outcomes in deceased donor kidney transplantation remains controversial. This study is a retrospective analysis of all cadaveric renal allografts procured locally by our center over a 3-year period. Kidney pairs were identified in which one kidney underwent pulsatile perfusion and transplantation at our center, whereas the contra-lateral kidney underwent cold storage and transplantation at another center. Eighty-eight percent of the exported kidneys were six-antigen matches. Study outcomes included 1-year graft and patient survival, delayed graft function, and need for posttransplant dialysis. Recipients had similar demographic and disease characteristics. Survival for pulsatile perfusion and cold storage were 95% and 88% (graft, $P=0.43$) and 98% and 90% (patient, $P=0.36$), respectively. The incidence of delayed graft function was 5% and 35% ($P<0.01$), whereas posttransplant dialysis was 5% and 30% ($P<0.01$), for pulsatile perfusion and cold storage, respectively. These data support routine use of pulsatile perfusion.

Keywords: Renal transplantation, Pulsatile perfusion, Acute tubular necrosis, Delayed, Graft function.

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Organ availability remains the single greatest issue in transplantation. As such, organ preservation to maximize donor organ quality and expand the pool of potential donors has been an intense area of research. Within the realm of renal transplantation, pulsatile perfusion has been explored as a possible tool to improve kidney allograft availability and quality. Belzer and Kountz (*1*) described the use of hypothermic perfusion with human blood as a means of kidney allograft preservation for deceased donors. An early comparison of cold storage versus pulsatile perfusion showed no appreciable benefit in graft survival (*2*). In light of the complexity and cost associated with pulsatile perfusion, controversy developed regarding its use as a standard preservation technique. Since that time, it has remained the prerogative of the individual transplant center.

Interest in pulsatile perfusion has not waned. It has been used in numerous studies to evaluate the quality of potential kidney allografts with mixed results (*3–6*). In addition, various additives, including glutathione and allopurinol, have been used in an attempt to rehabilitate potential kidney allografts that would have otherwise not been used (*7–11*). Most recently, it has been studied as a technique to allow for increased use kidney allografts from expanded criteria donors and donation after cardiac death (*12–14*).

In light of this work, the use of pulsatile perfusion as a standard form of renal allograft preservation remains controversial. There exists little consensus among the data. Advocates of this technique point to improved short-term clinical outcomes with the possibility of prolonged graft function (*15–17*). Critics claim that there is no significant improvement in graft function despite the significant cost and effort involved (*18*, *19*). This study is a retrospective, paired kidney analysis of the posttransplant function of 80 renal allografts procured by our center and preserved with pulsatile perfusion or cold storage.

METHODS

This study is a retrospective analysis of all cadaveric renal allografts procured locally by our center between January 2002 and December 2004. Four hundred forty-eight donors were procured by our center during this time period. All kidneys procured by our center undergo pulsatile perfusion during preservation and none were discarded during this analysis. All kidney pairs in which one kidney was transplanted at our institution and the contra-lateral kidney was sent to another transplant facility were identified. In all cases, the organ that remained at our center underwent pulsatile perfusion during preservation, whereas the paired kidney underwent simple cold storage during preservation. The United Network for Organ Sharing (UNOS) database was queried to obtain demographic and outcomes data for recipients of each kidney. Demographic data included age, sex, race, and cause of end-stage renal disease. Donor data were inherently controlled by the paired kidney study design. Transplant data points for analysis included cold ischemia time, need for posttransplant dialysis, 1-year graft survival, and 1-year patient survival. Minimum follow-up time was 1-year. Need for dialysis was defined as any posttransplant dialysis before discharge. Delayed graft function and graft failure were defined according to the UNOS guidelines and were extracted from the UNOS database as reported by the individual transplant center. Delayed graft function is defined as the requirement of immediate posttransplant dialysis, failure to produce urine output greater than 40 mL in the first 24-hr posttransplant, or less than a 25% decline in creatinine within the first 24-hr posttransplant. Graft failure is defined as a permanent return to dialysis after transplantation. These data were analyzed us-

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ing the chi-square test or the Student's *t* test for categorical and continuous variables, as appropriate. Kaplan-Meier survival curves were constructed to model survival outcome with Log rank testing used to assess for group differences. All research was conducted with approval of the Indiana University Institutional Review Board.

Preservation

All kidneys were flushed in situ with University of Wisconsin or Histidine-Tryptophan-Ketoglutarate solution (*20*). Organs were then procured in standard fashion and placed in cold storage using the flush solution at 4°C. All donors received mannitol before flush. Organs transplanted at our center were flushed with a modified University of Wisconsin solution, mechanical perfusion solution (Belzer-MPS, Trans-Med Corp, Elk River, MN) (*21*). Organs were then perfused on a Waters perfusion machine. Initially, organs were perfused at systolic and diastolic pressures of 60 and 40 mm Hg, respectively. Systolic pressures gradually declined during perfusion to an approximate nadir of 40 mm Hg. Goal perfusion rate was greater than 100 mL/min, though not all organs reached this rate. Organs were maintained under these conditions at 8°C until transplantation. No organs were discarded using these parameters. Recipients received mannitol before reperfusion. Organs to be shipped to another transplant center were maintained in cold storage at 4°C in the original flush solution. No other aggressive measures were undertaken to improve early graft function.

RESULTS

Forty kidney pairs fitting the inclusion criteria for this study were identified. Eleven kidneys transplanted locally were transplanted simultaneously with pancreas allografts. Thirty-five of the 40 allografts were sent to another institution for recipients with a six human leukocyte antigen-haplotype match. The other five kidneys were exported because of decline by all local centers. Recipient characteristics are described in Table 1. There were no significant differences in recipient characteristics between the two groups. Donor characteristics are described in Table 2. Average cold ischemia times were 18 hr for pulsatile perfusion and 17 hr for cold storage ($P=0.58$).

Outcomes

Kaplan-Meier graft and patient survival are depicted in Figures 1 and 2. The local and export groups did not differ statistically in survival at 1-year for either analysis, though there is a clear separation of the survival curves by the 1-year endpoint. Renal allograft survival was 95% and 88% at 1-year for pulsatile perfusion and cold storage, respectively ($P=0.43$). Patient survival was 98% and 90% at 1-year for pulsatile perfusion and cold storage, respectively ($P=0.36$). Delayed graft function was 5% and 35% for pulsatile perfusion and cold storage, respectively ($P<0.01$). Finally, the need for dialysis was 5% and 30% for pulsatile perfusion and cold storage, respectively ($P<0.01$) (Table 1).

TABLE 1. Demographic and outcome data for paired renal transplant recipients between January 2002 and December 2004

Demographics	Pulsatile perfusion	Cold storage	*P*
Age (yrs, mean)	44	46	0.56
Race			0.21
White	31	26	
African American	8	9	
Other	1	5	
Gender			0.82
Female	16	17	
Male	24	23	
Cause of ESRD			0.05
Diabetes mellitus	21	9	
Hypertension	5	8	
Glomerulonephritis	3	5	
Other	11	18	
Outcomes			
1-yr graft survival	95%	88%	0.23
1-yr patient survival	98%	90%	0.16
Delayed graft function	5%	35%	<0.01
Need for dialysis	5%	30%	<0.01

For each matched pair, one kidney was preserved with pulsatile perfusion and the contra-lateral kidney was preserved with cold storage only.
ESRD, end-stage renal disease.

TABLE 2. Demographic data for paired renal transplant recipients donors between January 2002 and December 2004 included in this study

Demographics	n (%)
Age (yrs, mean)	34
Race	
White	36 (90%)
African American	2 (5%)
Other	2 (5%)
Gender	
Female	13 (33%)
Male	27 (68%)
Type	
SCD	38 (95%)
ECD	2 (5%)
Preservation solution	
UW solution	14 (35%)
HTK solution	26 (65%)

SCD, standard criteria donor; ECD, extended criteria donor; UW, University of Wisconsin Solution; HTK, histidine-tryptophan-ketoglutarate solution.

DISCUSSION

The routine implementation of pulsatile perfusion in renal allograft preservation remains controversial. Large animal data exists suggesting that pulsatile perfusion in allograft preservation results in earlier return of renal function (*22*). Conflicting data exists in human studies; some studies show a decreased need for dialysis, whereas others have shown no improvement in graft function (*2*, *15–19*, *23*). This study eval-

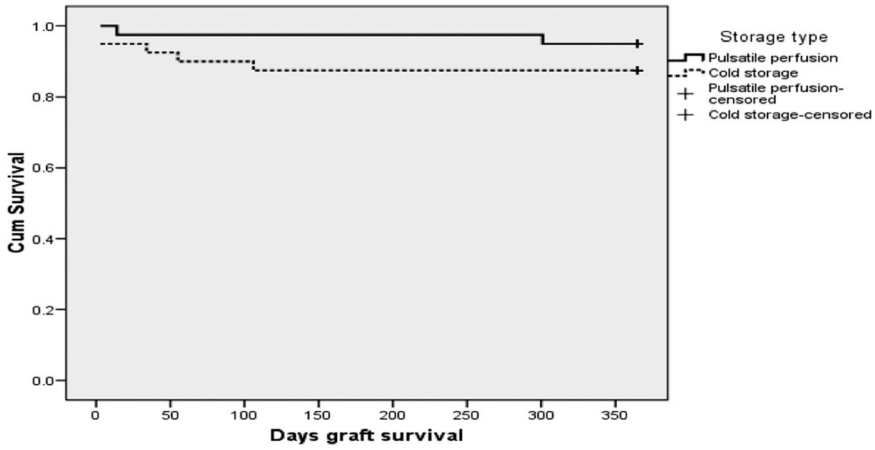

FIGURE 1. Kaplan-Meier graft survival postrenal transplant for 80 paired kidneys, 40 undergoing mechanical pulsatile perfusion and 40 receiving cold storage alone. Log rank $P=0.23$.

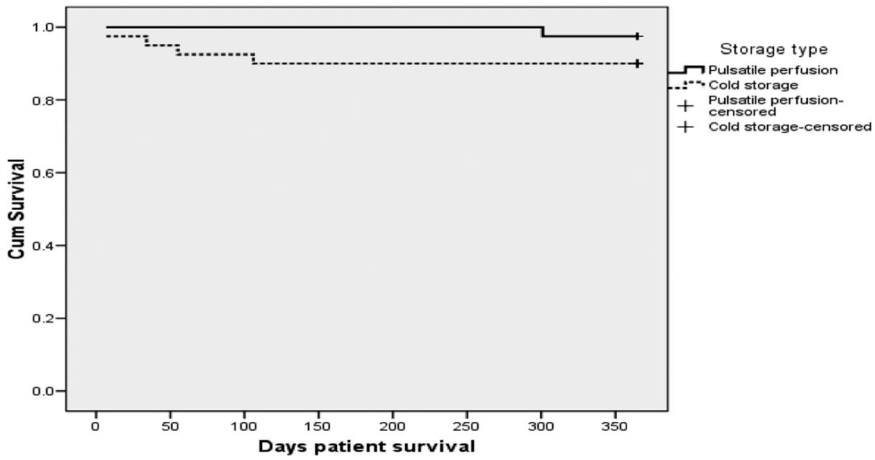

FIGURE 2. Kaplan-Meier patient survival postrenal transplant for 80 paired kidneys, 40 undergoing mechanical pulsatile perfusion and 40 receiving cold storage alone. Log rank $P=0.16$.

uated a paired kidney experience and evaluated the impact of pulsatile perfusion on posttransplant allograft function and short-term graft and patient outcomes. To control our analysis, we used donors in which one kidney was transplanted at our center and underwent pulsatile perfusion during preservation, whereas the contra-lateral kidney was sent to an outside institution and underwent simple cold storage. Each paired kidney was presumably at the same risk for delayed graft function and graft failure, given that they shared the same donor characteristics, procurement technique, and cold ischemia time. These matched kidneys were then transplanted into recipients with similar demographics. Importantly, 88% of kidney allografts that underwent cold storage were transplanted into recipients with a six antigen human leukocyte antigen match. These allograft-recipient matches represent an immunologically favorable destination for these donor kidneys and should result in improved outcomes for these recipients. Although the cold storage kidneys were exported, the total cold ischemia time for the two groups did not differ because transplantation of local kidneys was generally performed electively the day after procurement.

Given these circumstances, the use of pulsatile perfusion seems to significantly impact posttransplant renal allograft function. There was a statistically significant decrease in delayed graft function and in the need for dialysis for kidneys maintained with pulsatile perfusion. It has been shown that delayed graft function translates into worse outcomes for renal transplant recipients (*24*). Although the pulsatile perfusion group did not show a statistically significant improvement in patient and graft survival, factors that affect these outcomes, including degree of antigen match and cold ischemia time, favor the cold storage group. Even if the advantage for pulsatile perfusion were confined to the immediate posttransplant period, it would likely result in a more cost-effective therapy because of a decreased length of hospital stay and a decreased use of dialysis posttransplant. Unfortunately, these outcomes cannot be determined from these data. The median cost for pulsatile perfusion for each kidney at our center is $1000.

This study is one of only a few controlled studies examining the impact of pulsatile perfusion on early graft function and graft and patient outcomes. We have identified three other controlled studies that have examined this issue (*15*, *19*, *25*). These studies, although contradictory in result, were completed in the era before the use of tacrolimus and routine induction therapy. In addition, these studies showed substantially higher rates of acute tubular necrosis as compared with those found in our study. In addition to our study, only Alijani et al. and Merion et al. controlled for donor characteristics by splitting kidney pairs, allocating one to cold storage and the other to pulsatile perfusion. Although there is not consistency among these data, our study is the only one conducted in the modern era of renal transplantation.

Unfortunately, this study suffers from the limitations inherent to all retrospective studies with a small number of patients. The data are dependent on center reporting, which may be inaccurate. Additionally, there may be a center effect as all export kidneys were pooled for analysis, though they were transplanted at 37 different centers. All of the transplants using mechanically perfused kidneys were performed by one of our center's four kidney transplant surgeons. Despite these limitations, this study clearly suggests that pulsatile perfusion has a beneficial impact on early posttransplant graft function. This may translate into improved long-term graft and patient survival, though a study with more patients and longer follow-up is required to evaluate this question.

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