Cold Heparinized Lactated Ringers With Procaine (HeLP) Preservation Fluid in 266 Living Donor Kidney Transplantations

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Since the 1960s simple inexpensive cold lactated Ringers with additives has been used for short-term cold preservation of kidneys from living donors. We performed 266 living donor kidney transplantations from January 22, 2003 to October 30, 2006. Donor allografts were recovered laparoscopically and flushed with cold heparin, lactated Ringer's and procaine (HeLP) solution. Warm and cold ischemic times were typically <45 min and <90 min, respectively. The mean follow up was 21.6±12.2 months. There was no delayed graft function. Actuarial 1-year patient and graft survival were 98.6% and 98.1%, respectively. The creatinine at 1 year was 1.46±0.51 mg/dL. The cumulative incidences of acute cellular rejection at 6, 12, 18, and 24 months were 3.0%, 7.1%, 10.2%, and 11.7%. There were no identifiable side effects attributed to the HeLP solution. This study documents the effectiveness of cold HeLP as a flushing and short-term preservation fluid for living donor kidney transplantation with excellent results and significant cost benefit because of its low cost.

Keywords: Alemtuzumab pretreatment, Laparoscopic live donor nephrectomy, Tacrolimus monotherapy.

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The shortage of organs remains an ongoing problem in transplantation. Another important issue in transplantation is the ever-increasing medical expenses associated with it. Although it is important to reduce costs, it is important that outcomes are not affected. One potential area of cost savings is the use of a simple preservation fluid in living donor kidney transplantation because of the associated short warm and cold ischemia times.

Lactated Ringer's (LR) was one of the first preservation fluids to be used in transplant surgery, but was replaced by Collins, ViaSpan (Belzer UW), Custodiol HTK, and others. These solutions were developed with the goal of reducing organ damage and ischemia/reperfusion injury, including cellular swelling, oxygen-free radical injury, and cell membrane destruction. For example, lactobionate and gluconate are impermeable anions that prevent cellular edema and act as buffers to maintain the pH, adenosine provides adenosine tri-phosphate (ATP) as a source of energy for cell metabolism, steroids and other substances act to stabilize lysosomal membranes, and lidocaine prevents postischemia vasoconstriction and escalation of anaerobic respiration in the cells. On the other hand, with the short ischemia times in living-donor kidney transplantation, we had had a 19-year experience with the use of a simple and less expensive solution, LR, with two inexpensive additives, heparin and procaine (*1*). We looked at our recent experience with this HeLP (10,000 U heparin, 1 L of lactated Ringer's, and 100 mg procaine) solution, in living donor kidney transplantation.

PATIENTS AND METHODS

Between January 22, 2003 and October 30, 2006, a total of 266 consecutive laparoscopic (*2*) live donor nephrectomies resulting in 266 living donor kidney-only transplantations were performed at the University of Pittsburgh Medical Center Starzl Transplantation Institute (UPMC STI) (*3*). All donors were given heparin 3,000 units intravenously at least 3 min prior to clamping of the renal vessels. All kidneys were immediately placed into an iced saline bath and flushed with cold (5°C) HeLP solution until the effluent was clear. All recipients received pretreatment with a single dose of 30 mg of intravenous alemtuzumab and posttransplant tacrolimus monotherapy.

Modification in the timing and dosage of conventional immunosuppression in this regimen was submitted to the University of Pittsburgh Institutional Review Board, which judged the changes to be within the boundaries of historically based standard treatment. The use of HeLP in living donor kidney transplantation has been a standard of care practice at UPMC STI since 1987. The treatment protocols were reviewed by the University of Pittsburgh Medical Center Committee on Innovative Practices and by the Pharmacy and Therapeutics Practices Committee, with approval by both. All patients provided informed consent.

RESULTS

All kidneys functioned immediately; there were no cases of slow graft function, delayed graft function (DGF), or primary nonfunction. There was no vascular thrombosis. The mean human leukocyte antigen mismatch was 3.3±1.6. Actuarial 1-year patient and graft survival were 98.6% and 98.1%, respectively, and compared favorably with Organ Procurement and Transplantation Network/Scientific Registry of Transplant Recipients patient and graft survival rates of

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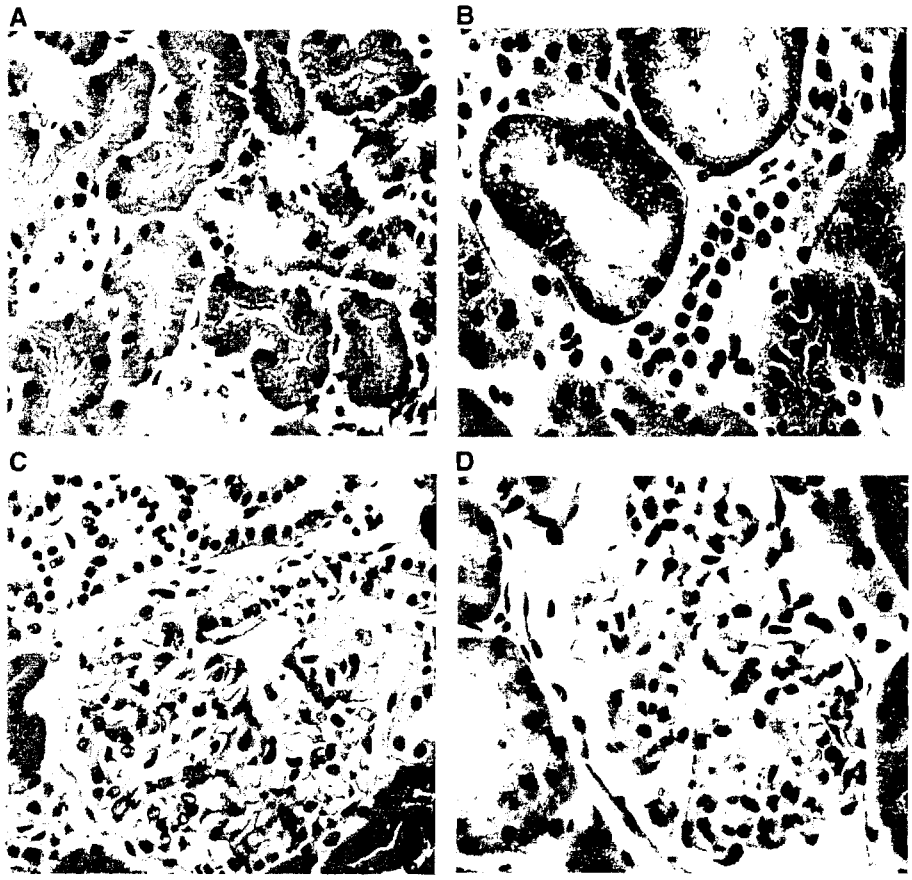

FIGURE 1. (A) Postdonation, pretransplant biopsy: normal preperfusion renal tubules flushed with HeLP solution. (B) Posttransplant biopsy: normal postreperfusion renal tubules without acute tubular necrosis. (C) Postdonation, pretransplant biopsy: normal prereperfusion renal glomeruli flushed with HeLP solution. (D) Posttransplant biopsy: normal postreperfusion renal glomeruli.

97.9% and 95.1%, respectively (*4*). The cumulative incidences of acute cellular rejection (ACR) at 1, 2, 3, 4, 6, 12, 18, and 24 months were 1.9%, 1.9%, 2.3%, 2.6%, 3.0%, 7.1%, 10.2%, and 11.7%, respectively. Most (>80%) episodes of ACR were Banff 1a or b and were sensitive to steroid pulses for treatment of rejection.

The mean donor hospital stay was 2.9±0.8 days and the mean recipient length of stay was 5.4±2.6 days. There were no allergic or any side effects (including heparin-induced thrombocytopenia and arrhythmias) attributed to HeLP. Despite the complexity of the recipient population, which included 37 retransplants, 4 human immunodeficiency virus–positive recipients, and 24 pediatric recipients, we achieved low ACR rates and excellent patient and graft survivals rates. Furthermore, good graft function was also observed, with a mean serum creatinine at 1 year and at mean 21.6 months follow-up of 1.46±0.51 mg/dL and 1.49±0.71 mg/dL, respectively. As shown in Figure 1, there was minimal inflammation in the tubules and glomeruli in the kidneys that were flushed and preserved with HeLP.

DISCUSSION

Cold ischemia is known to be associated with less allograft injury than warm ischemia (*5*). One unique characteristic in living donor renal transplantation is a short warm (typically <5 min for laparoscopic kidney extraction [this series includes up to five renal arteries] and about 30 to 45 min for the vascular anastomoses) and cold ischemia time (typically <1 hr). These short warm and cold ischemia times allowed us to continue the use of the cold (5°C) HeLP solution as a flushing and short-term preservation fluid with excellent results. Despite its long use at UPMC STI and at other transplant centers, this is the first report of using a rather simple cold preservation fluid (heparin and procaine in LR) that is both safe and cost-effective in living donor kidney transplantation.

Under nonischemic and nonhypothermic conditions, intracellular sodium is extruded through the sodium-potassium adenosine triphosphatase (*6*). Hypothermia and ischemia render this pump virtually nonfunctional. Intracellular sodium levels rise during ischemia, and are prevented by the sodium channel blocker procaine. Procaine also inhibits the activation of the enzyme phospholipase A, which has destructive properties on the cell membrane. This mechanism may be involved in the antiarrhythmic action of the drug and constitutes a potential for metabolic postischemic protection (*7*). Procaine is an ester anesthetic, metabolized in the plasma by the enzyme acetylcholinesterase (AChE). It is stable when freshly prepared and used immediately in slightly acidic cold HeLP solution (pH of heparin in LR is 6.28, and pH of procaine in heparin and LR is 6.22). AChE is a marker of red blood cell (RBC) membrane integrity, and determines RBC aggregation and deformability. During blood bank storage, improved preservation of RBCs is associated with a decrease

in AChE. Because procaine is an ester, it is hydrolyzed instantly on contact with blood by serum esterases. When administered in cold preservation fluid, the effects last through the ischemia period, but at organ reperfusion, it is washed out and metabolized rapidly (*8*). We used 0.1 g/L (*9*) of procaine because higher doses (e.g., 1 g/L) have shown to be toxic (*10*).

The patient cost for 1 L of HeLP is $2.83 (10,000 U heparin=$0.50, LR=$0.83, 100 mg procaine=$1.50). This is a significant cost reduction compared to the vendors' charges to the hospital of Viaspan ($282/L) and Custodiol HTK ($172/L). The use of LR with heparin and procaine is as effective as the more expensive Viaspan or Custodiol HTK solutions in living donor kidney transplantation because of the inherent short cold and warm ischemia times, thereby saving about $280 with ViaSpan or $170 with Custodiol HTK per patient, and potentially $1,200,000 to $1,800,000 (6,563 living donor kidney transplants were done in 2005 [*4*]) across the United States. Cold HeLP solution is obviously not a reasonable preservation solution for deceased donor kidney transplantation, but can be used safely for living donor kidney transplantation. It may also not be optimal in smaller transplant centers with long cold ischemia times, particularly in programs that do not have the benefit of two simultaneous operating rooms and may need to do the recipient after the living donor, thus entailing significantly longer cold ischemia times. The longest cold ischemia time in this series, however, was 5 hours.

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