CURRENT ISSUES IN ORGAN PRESERVATION
CLINICAL CASE STUDIES AND EXPERT COMMENTARY

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COURSE DESCRIPTION

Needs Assessment

Every effort is made to utilize each available organ for transplantation and to optimize subsequent patient and graft survival. Although there are many factors that impact immediate graft survival, a prominent topic continues to be the quality of organ preservation. Cold storage and specialized organ preservation solutions are used to minimize the damaging effects of cold ischemia and reperfusion on organ function.1

Optimal organ preservation is becoming increasingly important as the characteristics of donor organs change. Donor organs are being donated from older and sicker populations and being subjected to longer ischemia times.1 Increases in cold ischemia times are associated with higher graft loss across all organ types.2

Several different organ preservation solutions are currently used in the United States, and new solutions are under development. University of Wisconsin (UW) solution (ViaSpan®) has been the most widely used solution for multi-organ protection since its introduction in 1987. However, many institutions have begun to use Histidine Tryptophan Ketoglutarate (HTK) solution (Custodiol®) in their transplant practice. Several studies have shown HTK to be as effective as UW for liver, kidney and pancreas protection.3 5

Medicine Accreditation Statement

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Target Audience

This educational activity is intended for medical professionals involved in the management of transplant patients including: transplant physicians, surgeons, and organ procurement personnel.

Editors

Deanna Blisard, MD
Associate Professor of Surgery
Thomas E. Starzl Transplantation Institute
University of Pittsburgh
Pittsburgh, PA

A. Osama Gaber, MD
Director of Transplantation
Vice Chair for Administration and Faculty Affairs
The Methodist Hospital
Houston, TX

Ron Shapiro, MD
Professor of Surgery
Robert J. Corry Chair in Transplantation Surgery
Director, Kidney, Pancreas, and Islet Transplantation
Thomas E. Starzl Transplantation Institute
University of Pittsburgh
Pittsburgh, PA

Expert Commentators

John J. Fung, MD, PhD
Chairman, Department of General Surgery
Director, Transplant Center
Cleveland Clinic Foundation
Cleveland, OH

Charles Miller, MD
Program Director, Liver Transplantation
Cleveland Clinic Foundation
Cleveland, OH

David E.R. Sutherland, MD, PhD
Director, Diabetes Institute for Immunology and Transplantation
Professor, Department of Surgery
Head, Division of Transplantation, Department of Surgery
University of Minnesota
Minneapolis, MN
Faculty Disclosure

It is the policy of the University of Kentucky to ensure balance, independence, objectivity and scientific rigor in all of its educational activities. In accordance with the policy of the University of Kentucky, faculty are asked to disclose any affiliation or financial interest that may affect the content of this activity.

The faculty reported the following:

John Fung, MD, PhD has served on Essential Pharmaceuticals Speaker bureau
A. Osama Gaber, MD has received consultation fees from Essential Pharmaceuticals

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Development

The educational activity was developed by:

CTI Clinical Trial and Consulting Services
G. Mark Baillie PharmD, MHA
Senior Research Scientist
Eliezer Katz, MD, FACS
Vice President of Medical Affairs

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Learning Objectives

After completing this CME activity, participants will be able to:

1. Differentiate among commonly used solid organ preservation solutions.
2. Discuss factors that influence the outcome in organ preservation.
3. Describe the impact of organ preservation solutions on transplant outcomes.

INTRODUCTION

As the need for organ transplantation increases and the waiting list continues to grow, successful utilization and transplantation of as many available donor organs as possible has become paramount. While short-term outcomes have continued to improve and the incidence of acute rejection episodes has decreased, there has been only modest improvement in longer term outcomes, due to a variety of factors. Clearly, the greater use of extended criteria donors (ECD) and donation after cardiac death (DCD) donors should be considered as a contributing factor, which reduce both short and long-term graft survival. These donors contribute an increasingly larger percentage of organs for transplantation — older donors and DCD account for the major growth in deceased donors over the past 5 years. 1,2,6

The maintenance of organ viability during recovery and preservation remains a key factor in successful outcomes. Knowledge surrounding the impact of brain death, warm and cold ischemia, and reperfusion injury on post-transplant organ function has increased dramatically in recent years. 3,9

Increasing awareness of the effects of ischemia-reperfusion (I/R) injury on transplant outcomes has sparked a revived interest in cold storage preservation solutions. Optimal selection and use of preservation solutions to minimize the tissue damage and injury during the ischemic period to avoid post-transplant complications is an emerging area of research.8

The purpose of this monograph is to critically evaluate selected currently available and widely used preservation solutions in liver and pancreas transplantation based upon published literature. Case studies and expert commentary will be used to illustrate key considerations of the impact of organ preservation solutions on post-transplant outcomes and how this impacts the dynamically changing nature of organ donor utilization in the United States.
MECHANISMS OF TISSUE INJURY

Injury to a newly transplanted organ is caused by both prolonged cold ischemia and warm reperfusion following vascular anastomosis. At a cellular level, endothelial injury, leukocyte sequestration, platelet adhesion and unregulated coagulation contribute to mechanical graft damage (Figure 1).

Figure 1: Cellular and Subcellular Injury Associated with Ischemia-Reperfusion

Within as early as 4 hours following the interruption of blood flow to the organ (ischemia), 95% of cellular ATP stores are depleted. Cellular edema, necrosis, and apoptosis result from a series of molecular disruptions. Reperfusion is believed to be at least as damaging to the transplanted organ as cold storage. Increased production of reactive oxygen species (ROS) including superoxide (O$_2^-$) and hydrogen peroxide (H$_2$O$_2$) promotes lipid peroxidation and activation of endothelial cells. Activated endothelial cells release proinflammatory cytokines and upregulate their expression of adhesion molecules and Class II MHC proteins, leading to neutrophil influx. Loss of equilibrium among vasoactive substances including nitric oxide, endothelin and thromboxane A2, results in vasoconstriction, exacerbating tissue damage. Increased platelet activation and adhesion to the injured vascular endothelium also reduces blood flow and exacerbates ischemia.

The goals of cold storage prior to transplantation are to limit ischemia-reperfusion injury by inducing hypothermia, and reducing the evolution of ROS. However, a prolonged state of hypothermia may itself produce cellular edema through eventual depletion of ATP, and cell death through acidosis caused by effects on lysosomes. The three principal ingredients of storage solutions, namely colloids, buffers, and antioxidants, are included to counteract cellular edema, acidosis and the production of ROS, respectively.
STATIC COLD PRESERVATION SOLUTIONS

The mainstay of all clinically utilized preservation methods is the induction of hypothermia to reduce the metabolic requirements of the organ, and exsanguination of the microvasculature to facilitate optimal reperfusion. Specialty preservation solutions were developed to further extend acceptable cold ischemia times and to counteract the deleterious adverse effects associated with hypothermia. The method of flushing the organ with perfusate, immersing it in cold preservation solution, and keeping it at 4°C, has been used for more than 25 years and has shown to be a simple, easy way to transport and store an organ. Both new and current organ preservation solutions are constantly being evaluated and reformulated to find the optimal bridge to the ischemic gap during organ transport from donor to recipient.

Several solutions are utilized for static cold storage preservation of solid organs. Each solution may vary in composition; however, the goals of therapy with each solution are similar: to maximize organ function after reperfusion, to prevent cellular edema, and to delay cellular destruction. As such, essential components of current solutions prevent edema by being hyperosmolar and serve as buffers to maintain a proper pH balance. Free radical scavengers, calcium antagonists, complement regulators, and anti-platelet agents may provide additional protection from ischemia-reperfusion injury.

Preservation solutions have evolved throughout the years, with Euro-Collins, Marshall, and Ross-Marshall citrate solution being among the earliest solutions developed. A Scientific Registry of Transplant Recipients (SRTR) analysis from 2007 indicated that University of Wisconsin (UW) solution and Histidine Tryptophan Ketoglutarate (HTK) solution were used as the final flush solution in 63% and 28% of kidneys, respectively. The use of HTK has increased as the use of UW solution has decreased in the last three years. Since these two solutions represent approximately 90% of preservation solution use, they will serve as the focus of this comparison.

University of Wisconsin (UW) Solution

University of Wisconsin solution was initially developed as an experimental pancreas transplant preservation solution, but has been widely used for preservation of kidney, pancreas and liver transplanted organs since the late 1980s. It has also been used successfully in heart and intestinal transplantation.

The composition of UW solution was developed through systematic experiments designed to understand the principles of organ damage and protection mechanisms. The components of UW, as illustrated in Table 1, include buffers, adenosine, oxygen radical scavengers, and the colloid carrier hydroxyethyl starch (HES) (Table 1). The two metabolically inert components with relatively large relative molecular size, lactobionate and raffinose, serve as impermeable osmotic agents to delay and minimize cellular edema. HES is a non-toxic colloid used to prevent expansion of the extracellular space, the viscosity of the solution. Glutathione and allopurinol are included as free radical scavengers and adenosine is used as an adenosine triphosphate (ATP) precursor. Allopurinol is a xanthine oxidase inhibitor that has a protective effect when used before an ischemic insult. The omission of glucose is intended to minimize intracellular acidosis. UW solution was conceived as an intracellular preservation solution, with a high potassium and low sodium concentration to mimic an intracellular environment. UW solution has an osmolality of 320 mOsm/L and a room temperature pH of 7.4.

Although UW has been the historical standard preservation solution of choice, recent research has suggested potential disadvantages, in addition to a relatively high cost. High viscosity caused from the 5% HES included in UW has been reported to result in poor initial perfusion of the graft. The relationship of viscosity of a solution to temperature demonstrates that the viscosity of UW at 4°C is three times greater than a crystalloid solution such as water. This may also be exacerbated by the presence of the inert macromolecules within UW, that precipitate at colder temperatures, potentially lodging within capillaries and causing poor regional perfusion. Additional evidence demonstrates that the insulin within UW solution may exacerbate hepatic I/R injury by accelerating the depletion of the graft’s ATP supply.

Histidine Tryptophan Ketoglutarate (HTK) Solution

HTK was originally developed and introduced as a cardioplegia solution for open heart surgery in the 1970s. It was subsequently found to be effective in liver, kidney, and pancreas organ preservation. HTK is composed of the potent buffer histidine and two additional substrates, tryptophan and ketoglutarate (Table 1). The buffering action of histidine retards the decline in tissue pH during ischemia. Tryptophan, an amino acid, acts as membrane stabilizer and free radical scavenger. Another amino acid, ketoglutarate, serves as a substrate for anaerobic metabolism during preservation. In contrast to UW solution, HTK solution is an extracellular preservation solution with high sodium and low potassium concentrations. The electrolyte composition prevents triggering of energy consuming activation processes. A lowered concentration of potassium improves the washout of blood during organ recovery of by removing the vasoconstrictive effect associated with high potassium solutions.

Compared to UW solution, HTK has a much lower viscosity, even at temperatures seen during cold preservation. However, a concern surrounding HTK has been the large volume of solution historically utilized for organ preservation. Nevertheless, recent data suggests that lower volumes of HTK solution may be as effective. A recent case series investigation suggested safe organ preservation could be achieved without large volume infusion, based on similar clinical outcomes, with an average of 600mL additional HTK used, compared with UW solution.
Table 1: Composition of University of Wisconsin and HTK Cold Preservation Solutions\(^8, 13, 22, 24\)

<table>
<thead>
<tr>
<th>University of Wisconsin Solution (Viaspan)</th>
<th>Purpose</th>
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<tbody>
<tr>
<td><strong>Key Additives</strong></td>
<td><strong>Amount/Liter</strong></td>
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<tr>
<td>Potassium lactobionate</td>
<td>100 mmol/L</td>
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<tr>
<td>KH(_2)PO(_4)</td>
<td>25 mmol/L</td>
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<tr>
<td>Sodium</td>
<td>30 mmol/L</td>
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<tr>
<td>Raffinose</td>
<td>30 mmol/L</td>
</tr>
<tr>
<td>Adenosine</td>
<td>5 mmol/L</td>
</tr>
<tr>
<td>Glutathione</td>
<td>3 mmol/L</td>
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<tr>
<td>Allopurinol</td>
<td>1 mmol/L</td>
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<tr>
<td>Hydroyxethyl starch</td>
<td>50 g/L</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>8 mg/L</td>
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<tr>
<td>Insulin</td>
<td>40 U/L</td>
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<tr>
<td>Penicillin</td>
<td>200,000 U/L</td>
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<tr>
<td><strong>Estimated Cost/Liter</strong></td>
<td><strong>$282.00</strong></td>
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</table>

<table>
<thead>
<tr>
<th>HTK Solution (Custodiol)</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Key Additives</strong></td>
<td><strong>Amount/Liter</strong></td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>15 mmol/L</td>
</tr>
<tr>
<td>Potassium chloride</td>
<td>10 mmol/L</td>
</tr>
<tr>
<td>Magnesium chloride</td>
<td>4 mmol/L</td>
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<tr>
<td>Calcium chloride</td>
<td>0.015 mmol/L</td>
</tr>
<tr>
<td>Ketoglutarate</td>
<td>1 mmol/L</td>
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<tr>
<td>Histidine</td>
<td>198 mmol/L</td>
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<td>Mannitol</td>
<td>30 mmol/L</td>
</tr>
<tr>
<td>Tryptophan</td>
<td>2 mmol/L</td>
</tr>
<tr>
<td><strong>Estimated Cost/Liter</strong></td>
<td><strong>$181.00</strong></td>
</tr>
</tbody>
</table>

ATP: adenosine triphosphate; ROS: reactive oxygen species

There are additional preservation solutions in varying stages of development and use within transplantation. Celsior\(^24\) is a cold storage preservation solution used in a variety of organs including heart, kidney and liver.\(^24\) Polysol\(^25\) is a preservation solution that may have a potential impact in liver transplantation conditions.\(^25\) Institute Georges Lopez-1 (IGL-1) is a new clinically available solution, replacing UW’s HES with polyethylene glycol. IGL-1 also contains an extracellular component.\(^26\)
CLINICAL TRIAL REVIEW

University of Wisconsin solution has been considered the standard preservation solution in deceased donor abdominal transplantation. As new preservation solutions, such as HTK, have been introduced, comparison studies have been performed to identify similarities and differences in unique organ transplant donor and recipient populations. The following section will review selected recent clinical trials comparing HTK solution with UW solution, in both pancreas and liver transplantation.

Liver Transplantation

Despite experience in Europe dating back to the late 1980s, the first reported experience with HTK in liver transplantation in the United States came from the University of Pittsburgh in 2002.\(^2\)\(^7\) Since then, multiple studies comparing HTK to UW solution in liver transplantation have been published (Table 2).

Feng and colleagues conducted a systematic review to compare the safety and efficacy of UW and HTK solutions.\(^2\)\(^8\) They reviewed 10 published full text papers, including 11 comparisons in 1200 patients, in deceased donor and living related donor liver transplants, to assess patient and graft survival, liver function, and biliary complications. There were no statistically significant differences in patient survival, graft survival, primary non-function or acute rejection between UW and HTK. There was a statistically significant increase in bile production associated with HTK use (95% CI, 18.65-57.47; \(p=0.0001\)).

Chan and colleagues conducted a prospective study comparing safety and efficacy of UW and HTK solutions in a consecutive series of 60 right lobe adult-to-adult living donor liver transplants.\(^2\)\(^9\) Main outcomes were post-transplant liver biochemistry, prothrombin time, recipient morbidity, and graft and patient survival. There were no significant differences in the outcomes measures. The investigators suggested the low potassium content of the HTK offered logistical advantages. There may be less concern for the smaller amount of potassium entering the systemic circulation upon clamp release. In addition, the lower viscosity of HTK solution allows flushing of the hepatic artery on the back table by gravity alone, reducing the risk of intimal injury due to additional pressure.

A large case series comparing the perioperative and first year outcomes of liver transplantation using UW solution or HTK also demonstrated no significant differences in 1 month graft function and 12 month graft or patient survival.\(^2\)\(^9\) There was also no difference in the incidence of primary non-function (UW 1.5%, HTK 0.5%; \(p=NS\)). In contrast to previous reports using large volume flushes (10 to 20 L), in this case series, the HTK-preserved livers received an average of only 600mL more preservation than the livers preserved with UW (3800mL HTK vs. 3200mL UW). Because of this, the investigators suggested that large volume infusion of HTK solution may be unnecessary for safe organ preservation and may allow for even greater cost savings to be realized with HTK as compared to UW solution.

In a prospective single center analysis, Mangus and colleagues compared HTK and UW for immediate function and long-term transplant outcomes in whole organ DCD liver transplants (n=698), performing additional survival analysis on ECD subgroups.\(^5\) Fewer biliary complications were observed in the HTK group, including any need for biliary evaluation (HTK 51% vs. UW 60%; \(p=0.02\)) or the presence of bile duct stones or sludge (HTK 3.8% vs. UW 11%; \(p=0.001\)). The authors suggested that this may be due to improved flushing of the biliary microcirculation with HTK solution, as it is less viscous. There was no difference between the UW or HTK groups in graft loss within 7 days of transplant in either standard criteria donor or extended criteria donor donors. In addition, patient and graft survival and graft function were equivalent between ECD liver preserved with either UW solution or HTK solution.
<table>
<thead>
<tr>
<th>Author</th>
<th>Design/Population</th>
<th>Volume</th>
<th>GSR/PSR Results</th>
<th>Additional Results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mangus et al 2006</td>
<td>Comparison of first year outcomes of liver transplants using UW (n=204) or HTK (n=174)</td>
<td>UW: 3.2 ±1.4L</td>
<td>HTK: 3.8 ±1.0L</td>
<td>1-month: GSR: 92.0% PSR: 93.1%</td>
<td>PNF: UW 1.5% HTK 0.5% Higher Tbili in HTK group on post-operative days 1, 7, and 14, but similar to UW group by day 30</td>
</tr>
<tr>
<td>Chan et al 2004</td>
<td>Comparison of safety and efficacy of UW (n=30) vs. HTK (n=30) solutions in ALDLT liver transplants</td>
<td>Not reported</td>
<td></td>
<td>No difference in patient or graft survival (percentages not reported)</td>
<td>No difference in post transplant liver biochemistry, PT, or recipient morbidity</td>
</tr>
<tr>
<td>Mangus et al 2008</td>
<td>Prospective single center review of 698 liver transplants</td>
<td>UW: 3.2L</td>
<td>HTK: 3.8L</td>
<td>12-month GSR: SCD: 85% ECD: 82%</td>
<td>Higher initial AST and ALT levels (1st 7 days) in HTK group HTK showed better protection against biliary complications than UW</td>
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<tr>
<td>Feng et al 2007</td>
<td>Systematic review of literature from 1966 to June 2006 (10 articles)</td>
<td>All trials that reported cost/volume usage (n=4) showed increased volume usage and lower total cost with HTK</td>
<td>No difference found (RR=1.01; P=0.86)/(RR=1.01; P=0.07) (results include 2 trials)</td>
<td>Increased bile production was seen with HTK when compared to UW (weighted mean diff=-38.06; P=0.0001) (2 trials)</td>
<td>No statistically significant differences in GSR or PSR</td>
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</tbody>
</table>

ALDLT: adult-to-adult living donor liver transplant; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ECD: extended criteria donor; GSR: graft survival; HTK: Histidine-Tryptophan-Ketoglutarate solution; L: liter; NA: not applicable; NR: not reported; PNF: primary non-function; PSR: patient survival; PT: prothrombin time; SCD: standard criteria donor; Tbili: total bilirubin; UW: University of Wisconsin solution
Pancreas Transplantation

As in liver transplantation, there have been many studies comparing the use of UW and HTK solution in pancreas transplantation (Table 3). The initial reported comparison of HTK and UW in pancreas transplantation demonstrated similar efficacy in pancreas preservation.30

Table 3: Selected Trials Comparing UW and HTK Solutions in Pancreas Transplantation

<table>
<thead>
<tr>
<th>Organ</th>
<th>Author</th>
<th>Study</th>
<th>Volume</th>
<th>GSR/PSR Results</th>
<th>Additional Results</th>
<th>Conclusions</th>
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</thead>
<tbody>
<tr>
<td>PTA/PAK/SPK</td>
<td>Potdar et al 200431</td>
<td>Retrospective analysis of 33 patients up to 30 days after procurement to compare use of HTK (n=16) to UW (n=17)</td>
<td>NR</td>
<td>GSR: 94%</td>
<td>A trend of high amylase, high lipase and low glucose levels in the HTK patients</td>
<td>HTK and UW comparable</td>
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<td>PSR: 100%</td>
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<td>(p=0.49)</td>
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<td>GSR: 100%</td>
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<td>PSR: 100%</td>
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<tr>
<td>PTA/PAK/SPK</td>
<td>Alonso et al 200832</td>
<td>Retrospective review of outcomes at 2 centers after HTK (n=16) and UW (n=81) solution use between 2001 and 2007</td>
<td>HTK: 4.9 ± 1.2 L, UW: 2.6 ± 0.8 L (p &lt;0.01)</td>
<td>Not significantly different between groups</td>
<td>No correlation of flush volume and amylase, octreotide use (p=0.03), and graft pancreatitis (p=0.07) significantly higher in the HTK group compare to the UW group</td>
<td>Need controlled study to establish best practices Use caution with HTK volume, flush rates, and pressure</td>
</tr>
<tr>
<td>SPK</td>
<td>Becker et al 200733</td>
<td>Comparison in SPK transplants from January 2000 — April 2006</td>
<td>HTK: 9.65±2.00 L, (p&lt;0.01)</td>
<td>1-month GSR: 87.5%, PSR: 97.9%</td>
<td>Trend for higher peak lipase values on day 1 with HTK treatment</td>
<td>No statistically significant differences in pancreas or kidney GSR and PSR at 1 mos, 3 mos, or 1 year</td>
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<td>3-month GSR: 87.5%, PSR: 97.9%</td>
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<td>12-month GSR: 85.4%, PSR: 95.7%</td>
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<td>12-month GSR: 82.6%, PSR: 89.4%</td>
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<td>12-month GSR: 82.6%, PSR: 89.4%</td>
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<tr>
<td>PTA/PAK/SPK</td>
<td>Agarwal et al 200531</td>
<td>Single center updated pancreas transplant results</td>
<td>HTK: 3.4±0.8 L, UW: 3.9±1.0 L (p=0.26)</td>
<td>30-day GSR: 96%, PSR: 99%</td>
<td>No differences in fasting glucose, serial amylase and peak amylase between groups</td>
<td>No statistically significant differences in GSR or PSR on day 30 post transplant</td>
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<td>6-month GSR: 94%, PSR: 95%</td>
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<td>12-month GSR: 92%, PSR: 93%</td>
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<tr>
<td>PTA/SPK</td>
<td>Englesbe et al 200634</td>
<td>Retrospective, multi-center review in PTA, PAK, SPK transplants</td>
<td>Greater volume of HTK flush used per donor compared to UW (2L) (p&lt;0.01)</td>
<td>90-day Graft Function</td>
<td>Increased acute rejection with HTK at 180 days (HTK: 25.0% vs UW: 9.8%; p&lt;0.05)</td>
<td>HTK is a suitable substitute for UW in preservation of pancreas allografts</td>
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<td></td>
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<td>SPK: 86.4%</td>
<td>No difference in amylase or lipase in immediate post-operative period</td>
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<td>PTA: 85.7%</td>
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<td>(p=NS)</td>
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<td>90-day Graft Function</td>
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<td>SPK: 87.5%</td>
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<td>PTA: 94.1%</td>
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<td>(p=NS)</td>
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</table>

GSR: graft survival rate; mos: months; NR: not reported; NS: not significant; PAK: pancreas after kidney transplant; PSR: patient survival rate; PTA: pancreas transplantation alone; SPK: simultaneous pancreas and kidney transplantation

*historic controlled
An updated analysis from the same group compared 78 pancreas transplants flushed with HTK compared to historical controls preserved with UW (n=10). Comparable 30-day and 1-year patient and graft survival, along with similar fasting blood glucose and serum amylase levels at all post-transplantation intervals were demonstrated. Thirty day and 1 year patient survival with HTK was 99% and 93%; graft survival was 96% and 92%. There were no cases of primary non-function.

Controversy exists regarding the use of HTK in pancreas transplantation due to the larger volume of HTK needed and the susceptibility of the pancreas to edema. However, comparable graft function and patient and graft 30-day survival was reported by Potdar et al. in UW preserved (n=17) versus HTK preserved (n=16) pancreas transplants. Subjective observations recorded during back table preparation and after reperfusion noted that pancreas allografts flushed with HTK were more edematous, although pancreatitis was seen with equal frequency (HTK, 23%; UW, 18%; p = 0.71). It should be noted that this study utilized larger volumes of HTK than the Indiana experience.

A retrospective review of pancreas transplants included SPK, PTA, and PAK; from 2 transplant centers (n=97) flushed with either HTK (n=16) or UW solution (n=81) revealed a greater rate of graft loss due to thrombosis in the HTK group (3/16; 19%) than in the UW group (3/81; 4%) (p=0.05). The authors stated that they did not necessarily believe that HTK solution inadequately replaced UW in pancreas transplantation, but that caution should be used with respect to the volume of flush, flush rate, and pressure when using HTK.

Interestingly, Englesbe et al observed more acute rejection during the first 6 months post-transplant with HTK compared to UW solution (25% vs. 9.8% in pancreas transplants overall; 27% vs. 0% in SPK transplants; both p < 0.05). However, there were similar outcomes reported with respect to technical graft loss, 90 day graft function, and rate of pancreatic leak/abscess. In addition, there was no significant difference between the 2 groups in postoperative amylase and lipase.
CASE STUDIES: PANCREAS TRANSPLANTATION

As evidenced by the clinical trial comparisons of HTK and UW solutions previously described, it is often challenging to translate the results of these studies into clinical practice.

The following case studies describe actual patient experiences. While we agree that it is somewhat difficult to ascribe particular patient and graft outcomes in complex solid organ transplant recipients to the choice of cold storage preservation solution, these case study descriptions and their associated expert commentaries highlight important current clinical considerations in differentiating among preservation solutions.

Case Study 1

KB is a 52 year old female with end-stage renal disease secondary to Type 1 diabetes mellitus. She underwent her second simultaneous kidney-pancreas transplant on August 1, 2007.

Patient Medical History

The patient received her first simultaneous pancreas-kidney transplant 5 years earlier utilizing a standard UW flush and preservation protocol. The pancreas failed due to pancreas thrombosis in the early postoperative period and was removed. Renal allograft failure due to chronic tubular atrophy/interstitial fibrosis occurred after repeated episodes of acute cellular rejection and frequent urinary tract infections. She required daily insulin therapy and had increasing renal dysfunction prior to her second transplant, but had not yet returned to hemodialysis.

Donor Information

The donor for the second simultaneous pancreas-kidney transplant was a 26 year old male who had been in a motor vehicle accident and had sustained lethal intracranial hemorrhage and was declared brain dead. The donor was from the local organ procurement area. The cold ischemia time for the pancreas was 15 hours 23 minutes; for the kidney, cold ischemia time was 18 hours 21 minutes. In situ flushing and cold preservation for both organs were with 7-8 liters HTK solution as per local practice. The flush after the pancreas back table was with approximately 300mL of HTK solution.

Transplant Course

The transplant surgical procedure was uneventful. Both pancreas and kidney had good function in the early post-transplant period. Insulin was never needed post-transplant. The patient was preconditioned with alemtuzumab. Tacrolimus monotherapy was initiated as maintenance immunosuppression.

Post-operatively, the patient developed a urinary tract infection and pneumonia and required inpatient rehabilitation due to severe deconditioning. Both allografts continued to function well. She experienced one episode of pancreas rejection, which was successfully treated with a corticosteroid bolus and recycle, and the addition of mycophenolate mofetil to the maintenance immunosuppressive regimen.

The patient remains off insulin therapy or oral hypoglycemic agents. Laboratory values at her one year follow-up visit were serum creatinine 1.1 mg/dL, BUN 19 mg/dL, fasting blood glucose 92 mg/dL, amylase 74 U/L, and lipase 62 U/L.
Case Study 2

JB is a 56 year old male with Type 1 diabetes mellitus since age 2. In August 2006, he underwent pancreas transplantation (pancreas after kidney) after receiving deceased donor kidney transplants in 1981 and in 2002.

Patient Medical History

In addition to Type 1 diabetes mellitus, the patient also had a past medical history of hypertension, rheumatoid arthritis, stroke, and coronary artery disease, with a previous myocardial infarction.

Donor Information

The donor was a 20 year old female deceased donor from Utah who was receiving 3 vasopressors prior to pancreas recovery. HLA matching showed 0 antigen mismatch. The pancreas cold ischemia time was 15 hours 39 minutes. Flushing and cold preservation were with HTK solution. However, the volume of in situ flush with HTK was not known as the pancreas came from an outside organ procurement organization. The back table flush was with approximately 300mL of HTK solution.

Transplant Course

The surgical procedure was uneventful. The patient was preconditioned with alemtuzumab and was placed on tacrolimus and mycophenolate mofetil maintenance immunosuppression. Postoperatively, the patient developed allograft pancreatitis with a peak lipase of 14,914 U/L. The lipase decreased to a low of 641 U/L on post-operative day 11, but elevated again with resumption of oral intake. The allograft was studied with ultrasound and CT scans and found to have a pseudocyst in the tail. This was managed conservatively with eventual resolution.

The recipient remains well, with labs from his two year follow-up visit showing a serum creatinine of 1.6 mg/dL, BUN 24 mg/dL, fasting blood glucose 111 mg/dL, amylase 66 U/L and lipase 174 U/L. He remains on no insulin.
Cold preservation of the pancreas evolved over the years and proved to be a challenge compared to the cold preservation of other solid organs. The vascular and parenchymal structure of the pancreas makes cold preservation less effective. Several cold preservation solutions have been used historically. At the University of Minnesota, pancreas perfusion preservation was initially performed using silica gel filtered plasma. Although this solution proved to be effective with good graft function post-transplantation, the inherent risks of disease transmission associated with the use of pooled human plasma was of great concern. UW solution was developed by Dr. Belzer and associates to address the challenges of preserving the pancreas for transplantation. We successfully used UW solution for about 18 years and moved to the use of HTK solution 2 years ago due to supply and cost considerations.

The two cases presented here from the University of Pittsburgh illustrate the current successful use of HTK solution for the cold preservation of a pancreas allograft. With the exception of this being a retransplant, the first case represents a straightforward SPK transplant. The cold ischemia time of 15 hours, which may seem somewhat long to some surgeons, is actually not excessive when compared to registry data. In an analysis of the International Pancreas Transplant Registry (IPTR), the pancreas preservation time was less than 12 hours in 40% of cases and greater than 24 hours in only 5%. A clear correlation between outcome and preservation time could be observed in SPK transplant (p=0.05), with the cutoff at more than 23 hours of preservation. In multivariate models, the difference was confirmed where a longer preservation time was associated with an increased hazard ratio (HR) of 1.35 (p=0.11) for overall SPK pancreas graft failure and 1.46 (p=0.18) for technical failure. This is in contrast to a solitary pancreas transplant where no impact of preservation time on overall graft failure or technical failure was observed. In addition, according to the IPTR analysis, donor age appears to have a greater impact on graft functional survival and technical failure rates than preservation. While we strive to keep the cold ischemia time of the pancreas as short as possible, our goal at the University of Minnesota is to transplant the pancreas in less than 24 hours.

The second case describes the recipient of another SPK transplant who developed allograft pancreatitis postoperatively. Early graft pancreatitis remains a common cause of technical failure after pancreas transplantation, with nearly 20% of patients affected in some series. Etiology of graft pancreatitis and thrombosis is considered multi-factorial. Suggested causes include reperfusion injury, mechanical stricture, trauma, donor obesity, and prolonged ischemia. Flush volume and pressure are also important risk factors for graft pancreatitis. In general, I believe larger volumes and higher flush pressures are detrimental. Volume and pressure of pancreas flush, however, may not always be easily controlled in the context of a multi-organ recovery.

There is a perception of a possible association between flush and preservation with HTK solution and an increase in the risk of pancreas graft pancreatitis and thrombosis. However, no clear or definitive determination can be made as there has been only one prospective comparison of HTK and UW solutions in pancreas transplantation; in the study no differences in outcomes were found. Most published experiences related to this issue are single-center, retrospective reviews with relatively small numbers of patients. A recent brief report from Alonso and colleagues attempted to determine whether there was a basis for suspecting a causal relationship. Other studies of HTK solution in pancreas transplantation have not observed an association between HTK and graft pancreatitis. At present, no evidence based claims can be made on the risk for post-transplantation pancreatitis when HTK has been used for cold preservation. It should also be noted that there is little evidence that there is less graft pancreatitis with UW solution. However, in a recent review of the UNOS database outcomes for pancreas transplants preserved in HTK versus UW Solution, HTK preservation was associated with an increased risk of graft loss (hazard ratio 1.30, p=0.01). Unmeasured confounding variables such as surgeon technique, volume of initial flush at the time of organ recovery, organ quality, differences in immunosuppression protocols, and actual causes of graft loss, emphasize the inherent limitations of a retrospective registry review on one hand and underscore the need for prospective randomized studies on the other.

As reviewed earlier in this monograph, most trials have demonstrated that the overall safety and efficacy of HTK solution is comparable to that of UW solution in pancreas transplantation.
CASE STUDIES: LIVER TRANSPLANTATION

Case Study 3

CD is a 47 year old male with end-stage liver disease secondary to Hepatitis C cirrhosis, complicated by hepatocellular carcinoma.

Patient Medical History

The patient was found to have four lesions in both the right and left lobes and was treated with two sessions of transarterial chemo-embolization in the subsequent 12 months. He was listed for liver transplant by his biological MELD score of 16, since he remained outside of Milan criteria. He underwent a deceased donation after cardiac death (DCD) transplant on August 14, 2007.

Donor Information

The donor was 48 year old DCD donor from outside the local OPO, but within the region, who fell from a loading truck and sustained skull fractures and blunt head trauma. The donor did not progress to brain death, but in light of the extensive brain injury, the family requested donation after cardiac death. The donor was not breathing above the ventilator, but was not on any vasopressors. A donor team was dispatched. Prior to extubation 30,000 units of systemic heparin was administered. The donor quickly succumbed and was pronounced dead 12 minutes later. After the required 3 minute standoff, recovery commenced with aortic cannulation and flush with 6 liters of HTK. During this time, venting of the vena cava was done trans-diaphragnically and the liver and kidneys were procured. In situ flushing and cold preservation for both organs were with HTK solution. The initial impression by the donor surgeon was that the liver was well perfused, although the right lobe remained somewhat firm. The kidneys were placed on the pump, as per local practice, and were transplanted unremarkably into two kidney recipients with immediate function and cold ischemia times of 21 and 26 hours. The cold ischemia time for the liver was 10 hours, 13 minutes.

Transplant Course

Upon exploration, there were five hepatocellular carcinoma lesions with gross macronodular cirrhosis and extensively vascularized adhesions to the anterior abdominal wall. The technical summary of the operation showed a piggyback operation without venovenous bypass, end-to-side cavocaval anastomosis, portal vein-to-portal vein end-to-end anastomosis, hepatic artery-to-hepatic artery anastomosis, and duct-to-duct anastomosis without T-tube. After portal vein revascularization, 20 mg of recombinant tissue plasminogen activator (rTPA) was instilled into the hepatic artery and clamped for 20 minutes. At this time, the hepatic artery was backbled and the liver re-arterialized.

Following revascularization, although there was minimal post-reperfusion syndrome, there was moderate fibrinolysis which was treated with coagulation factor replacement. At the end of the case, the liver was making modest amounts of bile and the serum lactate peaked at 4.4 mg/dL.

The following day, ALT peaked at 2,454 IU/L and the INR at 2.5, while the AST peaked at 9,219 IU/L on post-operative day 2. The total bilirubin peaked on post-operative day 7 at 21.5 mg/dL. A liver biopsy demonstrated moderate cholestasis with hepatocyte dropout consistent with moderate ischemia/reperfusion injury, without evidence of rejection. An endoscopic retrograde cholangiopancreatography (ERCP) demonstrated normal bile ducts without obstruction or leak and a biliary stent was placed after instrumentation. The bilirubin began to decrease immediately thereafter and the patient was discharged on post-operative day 14 with a total bilirubin of 8.8 mg/dL. By post-operative day 21, the bilirubin had dropped to 2.7 mg/dL and was normal by post-operative day 32. The patient was seen again for stent removal on POD 45 and the cholangiogram was normal. At the one year follow-up, the liver function tests were normal and magnetic resonance cholangiopancreatography (MRCP) revealed no evidence of biliary anomalies. There was no evidence of HCC recurrence on computed tomography (CT) imaging. HCV levels were 850,000 U/mL at one year and the one year protocol biopsy revealed minimal inflammation without fibrosis.
Case Study 4

The patient is a 52 year old male patient with end stage liver disease and cirrhosis due to hepatitis C virus infection.

Patient Medical History

A 2.5 cm solitary hepatocellular carcinoma (HCC) lesion had been identified within the left lobe of the liver during the pre-transplant evaluation. The HCC was treated with transcatheter arterial chemoembolization (TACE) and open radiofrequency ablation. The patient was admitted to the intensive care unit (ICU) and required intubation due to the development of intractable ascites and hepatic hydrothorax. Continued decompensation was evidenced by prerenal azotemia, renal failure and overall physical deconditioning. Pre-transplant imaging confirmed cirrhosis of the liver, identified a stable liver mass in the left lobe and raised the possibility of mesenteric vein/portal vein thrombosis. The MELD score was 27.

Donor Information

The donor was a 47 year old African American male with history of hypertension. The cause of death was intracranial hemorrhage. He had been receiving treatment for the hypertension for several years, with evidence of compliance. There was only mild elevation of liver enzymes following resuscitation. He was 5 foot, 7 inches tall and weighed 84 kg.

On visual inspection during organ recovery, the liver appeared to be of normal size and had adequate capillary refill. In situ flush and cold preservation was performed with 5 liters of HTK solution. The cold ischemic time was 6 hours.

Transplant Course

During the transplant procedure, massive portal hypertension was noted. Retro-caval dissection was deemed too dangerous due to the extent of collateralization. Pre-caval dissection was undertaken and the hepatic veins were controlled, allowing caval anastomosis in a piggyback fashion. Although the portal vein appeared to be partially patent by palpation, it was discovered to have cavernous transformation grade IV portal vein thrombosis when transected. This finding precluded direct portal anastomosis. Attempts to declot the portal vein were unsuccessful. Alternative revascularization on the superior mesenteric vein was also not possible as the clot had extended to the complete length of the superior mesenteric vein. Dissection around the renal vein was not possible because of the extensive collateralization and the presence of retroperitoneal adhesions related to the prior open radiofrequency ablation procedure. To achieve portal flow, arterialization of the donor portal vein from an accessory hepatic artery was performed. Arterial revascularization was performed using a supraceliac aortic graft that was anastomosed to the donor common hepatic artery.

This unusual revascularization procedure required an extended period of time during which the liver allograft remained in the surgical field, prior to reperfusion. The liver allograft sustained approximately 45 minutes of warm ischemic time until hepatic artery revascularization, as well as an additional 50 minutes of warm ischemia while the dissection and arterialization of the portal vein was completed. At the end of the transplant procedure, variceal banding was completed due to persistent portal hypertension. A double valve peritoneovenous Denver shunt was also placed.

Immediate graft function was observed post-transplant with peak AST and ALT in the 900-1100 IU/L range that recovered to normal in 72 hours. The patient was extubated in 24 hours and made an uneventful recovery until released from the hospital 11 days post-transplant. On follow-up six months post-transplant, the patient exhibited only minimal ascites, with excellent liver and kidney function.
EXPERT COMMENTARY: LIVER TRANSPLANT CASE STUDIES

John J. Fung, MD, PhD and Charles Miller, MD

UW solution has been the “gold standard” for liver preservation and is still widely used. The liver transplant cases presented illustrate the successful use of HTK solution in complicated cases. The increased use of HTK preservation solution in the last few years reflects a continuous search for better preservation techniques. At least two studies have recently documented a higher incidence of late biliary complications associated with the use of UW solution for liver preservation.29, 40 Beginning in 2002, the University of Pittsburgh was the first US liver transplant program to use HTK solution. The lower viscosity of HTK compared to UW solution offered a potential advantage in lowering biliary complication rates by providing for a better flush of the biliary system and its microvasculature. The increased use of ECDs and especially DCDs underscores the need for optimal preservation of the liver as a whole and the biliary system in particular.

In DCD, formerly known as non-heart beating donors (NHBD), the adverse outcomes associated with higher graft loss due to primary non-function and increased risk for biliary strictures, the use of HTK has been suggested to provide improved early graft survival and decreased biliary stricture rates, especially when combined with intra-arterial thrombolytic therapy.41, 42

The pathophysiology of graft dysfunction in DCD transplantation represents the most extreme manifestation of the ischemia/reperfusion pathway seen in preserved allografts, but magnified by varying degrees of microcirculatory thrombosis. The impact of this vascular stasis and thrombosis depends on the organ — with kidneys this is manifested by a high rate of acute tubular necrosis and delayed graft function; with liver, there is a higher incidence of macrovascular thrombosis, primary non-function leading to a higher rate of early retransplantation, and more concerning, an increased rate of late biliary strictures leading to increased morbidity and mortality. Recent experiences with crystalloid based preservation solutions combined with thrombolytic agents suggest that better outcomes can be obtained by enhancing microcirculatory integrity and minimizing post-perfusion microthrombosis.

The impact of DCD in liver transplantation has been assessed from the SRTR database.43 DCD graft survival was significantly lower than donor brain death grafts with 1- and 3-year graft survival of 70.2% and 63.3% for DCD recipients versus 80.4% and 72.1% for donor brain death graft recipients. Recipients of a DCD graft had a greater incidence of primary non-function (11.8 vs. 6.4%) and re-transplantation (13.9% vs. 8.3%) compared with DBD recipients. The experience with DCD in the era of a colloid based preservation solution (i.e. UW solution), which constitutes the bulk of the SRTR DCD experience, suggests that almost three times as many DCD livers (up to 35-50% of livers) will suffer from ischemic-type biliary strictures (ITBS) as compared to donor brain death donor livers.43 This is due to the unique nature of blood supply for the bile duct, which depends solely on hepatic artery blood supply via a vascular plexus assuring bile duct viability.43 In DCD, the mandated period of warm ischemia imposed during the declaration of death in the controlled DCD donor and during the logistical delays inherent in the process of consent in the uncontrolled DCD donor, leads to stagnation of blood in the microcirculation. Although heparin is permitted in many DCD procurements, removal of formed blood elements from the microvasculature is dependent on adequate flushing.

Since flow through a hollow vessel is inversely related to the viscosity to the third power, the more viscous UW solution is less likely to penetrate and adequately flush the biliary plexus, potentially leading to ITBS.44

Crystalloid based preservation solutions, such as Histidine-Tryptophan-Ketogluterate (HTK) and Celsior, have the physical advantage of being significantly less viscous than UW solution. In addition, UW solution has been shown to develop adenosine crystals at sub-zero temperatures, which can further cause microcirculatory complications.19 As a result, crystalloid solutions are more likely to flush stagnant blood from the microvasculature in DCD organs than colloid based preservation solutions. Indeed, HTK has been shown to be associated with lower rates of biliary strictures than UW solution and the use of HTK solution for liver preservation was validated in a large series of deceased donor transplants completed at Indiana University.23, 45, 46

If DCD livers are to be used in greater frequency, the outcomes will need to be predictably similar to standard donor brain death. How can this be achieved? Some hints can be derived from other clinical settings, as well as in animal and human DCD studies. The development of hepatic artery thrombosis (HAT) following liver transplantation is one of the most devastating complications, with a high risk of subsequent biliary tract ischemia and necrosis, resulting in a high rate of retransplantation. In 1996, in a series of 17 patients that developed HAT early after liver transplant, an approach of immediate thrombectomy with the use of thrombolytic therapy directly instilled into the hepatic artery and revascularization demonstrated that 88% of liver allografts could be successfully treated with long-term patency of the hepatic artery and more importantly, no patient developed ITBS.47
The research group from the University of Bonn demonstrated graft alterations including erythrocyte aggregation and thrombus formation, which affected equilibration of the preservation solution within the microvasculature preventing effective cold preservation in a rat NHBD model. The compromised microvascular perfusion and release of liver enzymes associated with the use of UW solution for the initial flushout of livers was markedly attenuated by the additional warm preflush with Ringer’s lactated solution containing streptokinase.44 Other animal models have also validated the use of thrombolytic agents in DCD.

Investigators at the University of Newcastle upon Tyne then conducted a double-blinded, randomized, controlled trial of streptokinase preflush or placebo in human DCD kidneys. Following declaration of cardiac death, a solution containing therapeutic doses of streptokinase was given prior to initiation of infusion of preservation solution, in this case, Euro-Collins solution. DCD kidneys were machine-preserved and transplanted within 24 hours of procurement. These investigators noted that kidneys from the streptokinase-treated donors had a significantly better appearance at procurement and there was a higher proportion of kidneys transplanted through the use of streptokinase (63.6% with streptokinase vs. 42.6% with placebo). Given that the majority of DCD were uncontrolled, the high incidence of delayed graft function was not surprising, but all streptokinase treated kidneys recovered function.

At our own center, we have utilized a protocol of tissue plasminogen activator (TPA) use along with systemic heparin, preferentially given in situ, before declaration of death, followed by preservation flush with HTK. In those instances where TPA or heparin cannot be used before declaration of death, heparin is given along with HTK and the liver is cold-preserved. After portal revascularization in the recipient and the liver is warmed, and 20 mg of TPA in a volume of 7 – 10 cc of normal saline is instilled into the donor hepatic artery and clamped for 20-30 minutes. The hepatic artery is then back-bled to allow excess TPA to be discarded in order to minimize its introduction into the recipient circulation.45 These practical experiences address some concerns, such as exacerbation of ischemia-reperfusion injury and enhancement of operative bleeding.

Relevant to the current cases is the finding that outcomes were good, even with cold ischemic time extending beyond 14 hours, and with the long warm ischemic times documented in Case 4. In the latter case, the use of HTK solution was associated with acceptable early graft function and good liver and kidney function at 6 months of follow up.

These two technically challenging cases illustrate the effectiveness of HTK preservation solution in liver transplantation and although studies have shown that outcomes are similar when either UW or HTK solution is used, the reduced viscosity and better microcirculatory penetration of HTK solution may represent an advantage especially in avoiding long-term biliary complications. In the future, however, large-scale clinical trials will be required to definitively evaluate the impact of different preservation solutions on graft function and on long-term biliary complications.

**CONCLUSION**

The consistent reality of organ shortage for transplantation is the motivator for the increased use of marginal donors (ECD and DCD). The use of marginal donors underscores the importance of effective and safe organ preservation techniques. Cold preservation of organs for transplantation utilizing various solutions has been the most common preservation technique. UW and HTK are the most common preservation solutions used. An overall assessment of the literature indicates that the use of UW and HTK solutions produce similar outcomes with respect to graft and patient survival.

The challenges in regards to preservation and early graft function are somewhat different between different organs and organ-specific consideration should be given to the use of any preservation technique and solution.

As discussed in this monograph, the use of a crystalloid preservation solution, like HTK, likely provides for improved cold preservation in liver transplantation, particularly in liver allograft from DCD donors. For pancreas preservation, most publications support the conclusion that both HTK and UW cold preservation solutions provide effective preservation with comparable outcomes. The recent retrospective analysis of the UNOS database, demonstrating a negative effect of HTK pancreas preservation as compared to UW, carries the deficiencies of a retrospective, multicenter analysis and underscores the need for prospective studies.

Technical advantages related to the lack of need for additives, and low viscosity may increase the appeal of HTK solution in certain transplant settings. However, according to package labels, only 6-8L of UW solution is required for perfusion, compared to 10-12L of HTK. Nevertheless, studies have documented the successful use of lower volumes of HTK, without compromising outcomes. In evaluating the cost of preservation fluids, acquisition, additives required for the use of UW solution, and total volume required must be considered.

In this activity, we have compared the composition, rationale for use, and outcomes of transplantation of the pancreas and the liver preserved with UW or HTK solutions. The lower osmolality and lower concentration of electrolytes and histidine buffer systems inherent to HTK solution may provide a theoretical rationale for the choice of the less costly preservation solution by some centers. Clinical data support the conclusion that outcomes are at least comparable following the use of either solution in pancreas or liver transplantation.

Careful analysis of both the advantages and disadvantages of preservation solutions for liver and pancreas transplantation has become important as the use of marginal donors (ECD and DCD) continues to increase.