Impact of Preservation Solution on Abdominal Transplant Outcomes

Zoe Stewart, MD, PhD, FACS
Associate Professor Transplant & Hepatobiliary Surgery
Surgical Director Kidney & Pancreas Transplantation
University of Iowa Organ Transplant Center
• Financial disclosures
  – None

• Conflict of interest disclosures:
  – PI for Novartis *Transform* Trial
  – Co-PI for Shire Viro-Pharma SHP616-302
  – Invited speaker for Waters Medical Systems
Goals of Organ Preservation

- Maximize organ function post-transplant
- Allow for organ transport and increased geographic access
- Allow time for recipient preparation
- Allow time for cross-match to be performed
Static Cold Storage

- Organs flushed with cold preservation solution and packaged in additional solution on ice until transplant

“Gold Standard” for abdominal and thoracic transplantation
Ischemia Reperfusion Injury

↓ \( \text{O}_2 \) leads to mitochondrial damage ↓ ATP

↓ ATP leads to ↓\( \text{Na}^+ / \text{K}^+ \)-ATPase function

\( \text{Na}^+ \) influx and cellular swelling

↓ ATP leads to \( \text{Ca}^{2+} \) channel dysregulation

\( \text{Ca}^{2+} \) influx and ROS generation

Lipid, DNA, and protein damage

\textit{Cell Death}
Organ Preservation Solutions

The “IDEAL” Solution:

- Prevents cell swelling and tissue edema
  *Hydroxyethyl starch, lactobionate, raffinose, mannitol, tryptophan*

- Maintains intracellular pH
  *Histidine*

- Provides substrates for generation of ATP, etc.
  *Adenosine, ketoglutarate, L-arginine*

- Prevents injury from oxygen free radicals
  *Glutathione, allopurinol, N-acetylcysteine*
Abdominal Organ Preservation Solutions

• University of Wisconsin (UW) solution has been the “gold standard” for abdominal organ procurement and preservation since 1988

• Reports of equivalent graft outcomes with UW and Histidine-Tryptophan-Ketoglutarate (HTK) led to increased HTK use in the US

** UW or HTK used for > 98% abdominal organ procurements in the US
Increased HTK Use for Abdominal Organ Recovery

*Especially Donation after Cardiac Death Transplants*

![Bar chart showing the percentage of HTK use for all donors and DCD donors from 2004 to 2008.](chart.png)

*American Journal of Transplantation 2009; 9: 286–293*
# UW versus HTK - Composition

## Table 1. Comparison of Constituents of UW vs HTK Solution

<table>
<thead>
<tr>
<th>Component</th>
<th>UW (mmol/L)</th>
<th>HTK (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na</td>
<td>30</td>
<td>15</td>
</tr>
<tr>
<td>K</td>
<td>120</td>
<td>9</td>
</tr>
<tr>
<td>pH</td>
<td>7.4</td>
<td>7.1</td>
</tr>
<tr>
<td>Lactobionate</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Glutathione</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Raffinose</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Hydroxyethyl starch</td>
<td>5 gm%</td>
<td></td>
</tr>
<tr>
<td>Adenosine</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Histidine</td>
<td></td>
<td>180</td>
</tr>
<tr>
<td>Tryptophan</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Ketoglutarate</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Mannitol</td>
<td>30</td>
<td></td>
</tr>
</tbody>
</table>

Potential Benefits of HTK

Reduced potassium levels = safer reperfusion

Reduced viscosity = better penetration of microvasculature

Reduced cost = despite increased volume
Does preservation solution impact liver allograft survival?
Early Studies in Liver Transplant


4 European transplant centers followed 214 patients receiving HTK-preserved liver transplants

**1 year graft survival 80% HTK (equivalent to historical UW)**


69 HTK-preserved compared to 68 UW-preserved liver transplants

**HTK 1 year graft survival (71%) versus UW (78%) (p=NS)**

**HTK much higher re-transplantation (13%) versus UW (7%)**
Early Studies in Liver Transplant


371 HTK compared to 327 UW preserved liver transplants

* No difference in 1 year graft survival (85%)

* Donation after cardiac death and CIT > 12h had reduced 1 year graft survival with HTK preservation
Histidine–Tryptophan–Ketoglutarate (HTK) Is Associated with Reduced Graft Survival in Deceased Donor Livers, Especially Those Donated After Cardiac Death

Reviewed UNOS database of liver transplants from July 1, 2004 to February 28, 2008 \( (N=17,428) \)

Exclusion criteria: 1. Recipient age < 18 years
2. Multi-organ transplant
3. Split graft
4. Living donor
5. Alternative solution
Study Hypotheses

1. Single center studies underpowered to detect differences in graft survival or generate stable multivariate models

2. Single center studies confounded by era effects between HTK cohort and historical UW controls

3. Single center studies may not be generalizable due to center-specific effects
## Liver Transplant Demographics

<table>
<thead>
<tr>
<th></th>
<th>UW (n=12,673)</th>
<th>HTK (n=4,755)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Transplant Characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cold ischemia time (h)</td>
<td>7.6</td>
<td>7.3</td>
</tr>
<tr>
<td>Share type - Local (%)</td>
<td>68.4</td>
<td>75.5</td>
</tr>
<tr>
<td><strong>Recipient Characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>52.6</td>
<td>52.9</td>
</tr>
<tr>
<td>Female (%)</td>
<td>31.8</td>
<td>31.8</td>
</tr>
<tr>
<td>Ethnicity - Caucasian (%)</td>
<td>71.6</td>
<td>77.0</td>
</tr>
<tr>
<td>Hospitalized (%)</td>
<td>29.7</td>
<td>25.5</td>
</tr>
<tr>
<td>On life support (%)</td>
<td>6.6</td>
<td>5.4</td>
</tr>
<tr>
<td>Prior transplant (%)</td>
<td>8.0</td>
<td>7.5</td>
</tr>
<tr>
<td>Status 1</td>
<td>6.7</td>
<td>4.7</td>
</tr>
<tr>
<td><strong>Donor Characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>41.9</td>
<td>41.6</td>
</tr>
<tr>
<td>Female (%)</td>
<td>40.4</td>
<td>40.7</td>
</tr>
<tr>
<td>Ethnicity - Caucasian (%)</td>
<td>65.1</td>
<td>75.1</td>
</tr>
<tr>
<td>Cause of death - ICH (%)</td>
<td>45.3</td>
<td>43.6</td>
</tr>
<tr>
<td>Donor after cardiac death (%)</td>
<td>4.5</td>
<td>5.3</td>
</tr>
</tbody>
</table>
Distribution of Liver Transplants by Center

**50% of liver transplants performed by 25 transplant centers**

*American Journal of Transplantation 2009; 9: 286–293*
Evaluation of Center-Specific Effects

1. Evaluated distribution of transplants among transplant centers

2. Evaluated the % HTK use as function of transplant center volume

3. Included transplant center volume in multivariate regression models

4. Performed clustered variance estimates to account for correlation of practice patterns by transplant center
HTK Use in Liver Transplant is Not Impacted by Center Volume

Multivariate Model for Graft Loss

Risk factors for graft loss determined with Cox proportional hazards models adjusted for:

**Recipient:** age, gender, ethnicity, primary diagnosis, BMI, albumin, diabetes, encephalopathy, hypertension, hospitalized, on life support, prior transplant, prior abdominal surgery, Status 1

**Donor:** age, gender, ethnicity, BMI, creatinine, diabetes, hypertension, cause of death

**Graft:** cold ischemia time, donation after cardiac death
# HTK Preservation is a Risk Factor for Graft Loss after Liver Transplantation

<table>
<thead>
<tr>
<th></th>
<th>Multivariate - Patient and Center Level*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>All deceased donor transplants</td>
<td>1.13 (1.03-1.24)</td>
</tr>
<tr>
<td>(n=4,755 HTK and 12,673 UW)</td>
<td></td>
</tr>
<tr>
<td>Donor after cardiac death</td>
<td>1.39 (1.07-1.81)</td>
</tr>
<tr>
<td>(n=254 HTK and 575 UW)</td>
<td></td>
</tr>
</tbody>
</table>
Kaplan-Meier Graft Survival Curves for DCD Liver Transplants

**HTK Increases Risk of Early (< 30 days) Graft Loss after Liver Transplantation**

<table>
<thead>
<tr>
<th>Condition</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All deceased donor transplants</td>
<td>1.19 (1.02-1.40)</td>
<td>0.031</td>
</tr>
<tr>
<td>(n=4,755 HTK and 12,673 UW)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cold ischemia time &gt;= 8 h</td>
<td>1.31 (1.08-1.60)</td>
<td>0.007</td>
</tr>
<tr>
<td>(n=1,491 HTK and 4,345 UW)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cold ischemia time &lt; 8 h</td>
<td>1.13 (0.91-1.33)</td>
<td>0.3</td>
</tr>
<tr>
<td>(n=2,540 HTK and 6,428 UW)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donor after cardiac death</td>
<td>1.63 (0.93-2.91)</td>
<td>0.09</td>
</tr>
<tr>
<td>(n=254 HTK and 575 UW)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donors Age &gt;= 70 years</td>
<td>1.67 (0.94-2.96)</td>
<td>0.081</td>
</tr>
<tr>
<td>(n=225 for HTK and 739 for UW)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Does preservation solution impact liver allograft survival?

YES!
Does preservation solution impact liver allograft survival?

- HTK use associated with significant reduction in graft survival
- Effect more pronounced for “less ideal” grafts: DCD, CIT > 8 hours, age > 70 years
- HTK use results in increased risk of early graft loss
Does preservation solution impact pancreas allograft survival?
Key Previous Studies - Pancreas


Multicenter (4) analysis 36 HTK-preserved compared to 41 historical UW-preserved pancreas transplants

**90 day graft survival 86% HTK versus 90% UW**

**HTK >> UW acute rejection (30.5% vs. 12.2%)**
81 historical UW-preserved and 16 HTK-preserved pancreas transplants

* 3 yr graft survival 70% HTK versus 90% UW

* HTK >> UW graft thrombosis (19% vs. 4%)
* HTK >> UW graft pancreatitis (56% vs. 23%)

* UW for 25 subsequent pancreas transplants resulted in no further graft thromboses and 100% graft survival at 1 year
Does preservation solution impact pancreas allograft survival?

- HTK use associated with significant reduction in graft survival for pancreas grafts (N=4392; HR 1.30, p=0.014)

- Effect more pronounced for “less ideal” grafts: CIT > 12 hours (HR 1.42, p=0.017)

- HTK use results in increased risk of early graft loss (OR 1.54, p=0.008)

Stewart, AJT 2009
Does preservation solution impact kidney allograft survival?
Key Previous Studies - Kidney


82 HTK-preserved and 241 UW-preserved kidney transplants

* CIT > 24h  HTK 50% delayed graft function versus UW 23.9%

* 1 year graft survival:  
  CIT > 24h = 77% HTK vs. 91% UW  
  CIT < 24h = 88% HTK vs. 93% UW

Opelz and Döhler (2007) *Transplantation* 83: 247-53 (Germany)

9,677 HTK-preserved and 53,560 UW-preserved kidney transplants from Collaborative Transplant Study project 1990-2005

* Relative Risk graft loss 1.42 HTK vs. 1.21 UW
Key Previous Studies - Kidney


317 HTK-preserved compared to 317 historical controls of UW-preserved deceased donor kidney transplants

* No significant difference in graft survival through 4 yrs

* Increased DGF with HTK

**Table 4:** Delayed graft function and technical graft failure in renal allografts

<table>
<thead>
<tr>
<th>Effect</th>
<th>Preservative</th>
<th>UW (n = 317)</th>
<th>HTK (n = 317)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deceased donors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delayed graft function</td>
<td></td>
<td>17.4%</td>
<td>26.2%</td>
<td>0.005*</td>
</tr>
<tr>
<td>Technical graft failure</td>
<td></td>
<td>0%</td>
<td>0.9%</td>
<td>0.249</td>
</tr>
</tbody>
</table>
Does preservation solution impact kidney allograft survival?

- HTK use associated with significant reduction in death-censored graft survival for kidneys (N=21,626; HR 1.20, p=0.008)

- No impact on delayed graft function (OR 0.99, p=0.7)

Stewart, AJT 2009
Potential Mechanisms

• HTK contains fewer antioxidants

• HTK lacks strong oncotic agent which may play a critical role in preventing tissue edema

*May be particularly critical for liver and pancreas
Preservation solution matters in abdominal transplantation

Impact more pronounced with less "ideal" donor grafts