REFERENCES

1) Custodiol HTK Solution PI available at http://www.custodiol.com/prescribing-info/


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15) Reddy KS, Moss A, Mekeel K et al., Pancreas Transplantation using HTK preservative: Is it a cautionary tale? ATC 2009 Poster Session June 1, 2009 Exhibit Hall C

CUSTODIOL® HTK SOLUTION

Custodiol ® HTK Solution is intended for perfusion and flushing of donor liver, kidney, pancreas (and heart) prior to removal from the donor for preserving these organs during hypothermic storage and transport to the recipient. It is based on the principal of inactivating organ function by withdrawal of extracellular sodium and calcium, together with intense buffering of the extracellular space by means of histidine/histidine HCl, so as to prolong the period for which the organs will tolerate interruption of blood and oxygen.

INTRODUCTION

CUSTODIOL® HTK SOLUTION

- Low Viscosity
- Low Potassium content safe for systemic absorption
- Low Sodium
- No Starch
- Buffered with histidine and histidine HCl
  - Doubles buffering capacity in transplanted organs which moderates drop pH
  - Protects against edema
  - Lower Biliary complications
  - No Flush needed

Organ Preservation Solutions: Major Clinical Differences

<table>
<thead>
<tr>
<th></th>
<th>HTK (Custodiol®)</th>
<th>UW (ViaSpan®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composition</td>
<td>K+ low</td>
<td>K+ high</td>
</tr>
<tr>
<td>Viscosity</td>
<td>(1°C) 2.0 cP, ~water</td>
<td>High: 6.2 cP</td>
</tr>
<tr>
<td>Flow</td>
<td>Higher:x3</td>
<td>Lower</td>
</tr>
<tr>
<td>Cooling</td>
<td>Faster</td>
<td>Slower</td>
</tr>
<tr>
<td>Additives</td>
<td>Ready-to-use</td>
<td>Several: fresh GSH</td>
</tr>
<tr>
<td>Filters</td>
<td>No</td>
<td>Yes: particles 3-25-&gt;100 μm</td>
</tr>
<tr>
<td>Flushing Prior to Implant</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Adverse events</td>
<td>None</td>
<td>Cardiovascular complications</td>
</tr>
<tr>
<td>In situ protection</td>
<td>Heart, kidney, liver</td>
<td>No</td>
</tr>
</tbody>
</table>

cP–centipoise
EXTENDED CRITERIA DONORS
In a study comparing HTK and U of W in a large number of SCD and ECD livers, the authors concluded that HTK and U of W are not clinically distinguishable in the large sample of liver transplants. However, HTK may be protective against biliary complications. Kaplan-Meier graft survival curves failed to demonstrate a significant difference in SCD or ECD livers.\(^{(7)}\)

A recent study concluded that Ischemic-type biliary lesions (ITBL) account for a major part of patients’ morbidity and mortality after orthotopic liver transplantation (OLT). This study retrospectively evaluated 1843 patients.\(^{(8)}\)

Organs that were perfused with University of Wisconsin (U of W) solution developed ITBL significantly more often than Histidine-Tryptophane-Ketogluterate (HTK) perfused organs \((P=0.036)\).\(^{(8)}\)

The authors of this study mentioned that the clinical consequences of this study for their institution have been the strict limitation of CIT to <10h and the exclusive use of HTK solution.\(^{(8)}\)

In a meta-analysis and systematic review on the effect of preservation solutions for liver transplant, the authors concluded there was no good evidence of any difference in outcomes when comparing HTK and either University of Wisconsin solution or Celsior.\(^{(9)}\)

### Early dysfunction comparing HTK with U of W solution in randomized controlled trials\(^{(9)}\)

<table>
<thead>
<tr>
<th>Author and Year</th>
<th>HTK n</th>
<th>HTK N</th>
<th>U of W n</th>
<th>U of W N</th>
<th>Relative Risk [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erhard 1994</td>
<td>0</td>
<td>30</td>
<td>1</td>
<td>30</td>
<td>0.33 [0.01, 7.87]</td>
</tr>
<tr>
<td>Meine 2006</td>
<td>1</td>
<td>37</td>
<td>6</td>
<td>65</td>
<td>0.29 [0.04, 2.34]</td>
</tr>
<tr>
<td>Brolese 2008</td>
<td>6</td>
<td>148</td>
<td>2</td>
<td>74</td>
<td>1.50 [0.31, 7.25]</td>
</tr>
</tbody>
</table>

Fixed Effects Model for All Studies

*Forest plot shows relative risk comparing U of W and HTK in randomized controlled studies (<1 favors HTK). \(Q =1.78, \ p = .041\)
**LIVING DONOR DATA**

In a study comparing HTK and U of W in Renal Transplantation, the authors concluded HTK demonstrated similar efficacy to U of W in terms of patient and graft survival. \(^{(10)}\)

HTK was associated with a significant risk reduction on the incidence of DGF.

- Graft survival did not significantly differ by preservation solution but in living donor patients, HTK showed a trend toward improved long-term graft survival over U of W solution.

**Figure A.**

**HTK versus U of W for Renal Transplant**

In a study looking at cost effectiveness of preservation solutions in live donor kidneys, it was shown that HTK is superior to LR for preventing DGF, HTK and U of W are more cost effective than LR and LRD in transplantation. \(^{(11)}\)

In a study by Argarwal et al., it was found that HTK is not inferior to U of W (as previously suggested by other authors) and may in fact be better protection for the prevention of delayed graft function compared to U of W solution. \(^{(12)}\)

**NON LIVING DONOR DATA**

In a randomized multi-center study on kidney graft preservation comparing HTK with U of W and Euro Collins, the authors concluded HTK is comparable to U of W in its preservative abilities. \(^{(13)}\)

**KAPLAIN-MEYER KIDNEY ALLOGRAFT**

In a study comparing HTK and U of W in Renal Transplantation, the authors concluded HTK demonstrated similar efficacy to U of W in terms of patient and graft survival. \(^{(10)}\)

**Figure B.**

Effect of initial graft function of graft survival in the U of W-HTK study.

The multivariate analysis of the U of W-HTK study showed that the kind of preservation solution used was not associated with INF. But four other factors were indeed associated with INF: donor age, donor cause of death, re-transplantation and cold ischemic period. \(^{(13)}\)

**Figures A & B - Survival after transplant using either U of W or HTK organ preservation solution. The hazard ratio refers to the risk of graft loss when HTK solution was used compared to U of W solution.**
A recent study prospectively evaluated early graft function in clinical pancreas transplantation after organ perfusion with HTK versus U of W. This prospective, randomized study, in concordance with the findings of previous retrospective comparisons of pancreas perfusion with HTK versus U of W solution demonstrated equally good patient and graft survival for both preservation fluids. HTK solution appears to be equally suitable as U of W solution for \textit{in situ} perfusion and organ preservation in clinical pancreas transplantation\(^{(14)}\).

The study was designed as a phase III study for Germany.\(^{(14)}\)

This study looks at pancreas transplant outcomes. The authors performed 115 PTXs (simultaneous kidney PTX (SKPTs) and 28 solitary PTX’s (SPTs) in 114 patients between July 2003 and September 2008\(^{(15)}\).

### Outcomes in HTK v U of W Group

<table>
<thead>
<tr>
<th></th>
<th>HTK (n=75)</th>
<th>U of W (n=39)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 day P graft survival</td>
<td>93%</td>
<td>95%</td>
<td>NS</td>
</tr>
<tr>
<td>1 yr actual P graft survival (for pts w 1 yr FU)</td>
<td>89%</td>
<td>85%</td>
<td>NS</td>
</tr>
<tr>
<td>1 yr actual K graft survival (for pts w 1 yr FU)</td>
<td>95%</td>
<td>100%</td>
<td>NS</td>
</tr>
</tbody>
</table>

Conclusion – There is no difference in the kidney and pancreas graft survival rates between HTK and U of W preservation solutions in PTX recipients with cold ischemia times up to 15 hrs. \(^{(15)}\)

Normal endocrine function (no need for exogenous insulin) for patients with organs perfused with HTK \((n = 27)\) versus U of W \((n = 41)\) solution during the first 6 months after pancreas transplantation \((mo, months)\).
A recent study compared the effectiveness of HTK and U of W in the preservation of human pancreata intended for islet isolation. The authors concluded HTK and U of W possess equal capacity to prevent cellular edema throughout the pancreas procurement and isolation process.\(^{(16)}\)

The quality of pancreas flush and preservation is one of the most important determining factors for the successful grafting of both whole pancreata and isolated islets\(^{(16)}\).

Islet purity distribution across purification fractions. The number of isolations analyzed was 95 and 157 for HTK and U of W, respectively. Data was expressed as percentages and adjusted for age, sex, BMI, CIT and enzyme. Sample size ranged from 167-249 across fractions. Statistical significance was set at $p<0.01$.

The distribution of islet purity across fractions also served as an indicator of purification outcome and an indirect measurement of cellular edema. Within the top fraction (>69%), the islet purity distribution was similar between the HTK and U of W groups. However within the middle fraction (40-69%), a significantly higher purity was observed in fractions 6 and 7 if the HTK group.\(^{(16)}\)
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