# University of Wisconsin Versus Histidine-Tryptophan-Ketoglutarate for Tissue Preservation in Live-Donor Liver Transplantation

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***Objectives:*** **University of Wisconsin solution has twice the cold hepatic preservation time as does Euro-Collins solution. Histidine-tryptophan-ketoglutarate has a lower potassium content than does University of Wisconsin solution and is used more frequently. To date, however, studies comparing University of Wisconsin and histidine-tryptophan-ketoglutarate in live-donor liver transplantation are lacking. We therefore sought to examine the hepatic function of live-donor liver transplantation allografts preserved in University of Wisconsin solution as compared with those preserved in histidine-tryptophan-ketoglutarate solution.**

***Materials and Methods:*** **Between July 2003 and August 2004, 33 live-donor liver transplantations were performed at the University of Rochester Medical Center, Rochester, NY, USA. University of Wisconsin solution was used for the first 9 allografts, and histidine-tryptophan-ketoglutarate was used for the subsequent 24 allografts. Daily total bilirubin, aspartate amino transferase, amino alanine transferase, alkaline phosphatase, gamma glutamyl transpeptidase, and international normalized ratio levels were measured for the first 8 postoperative days. Peak values were compared between the groups.**

***Results:*** **There was no primary graft nonfunction in either group. Two patients in the histidine-tryptophan-ketoglutarate group developed hepatic artery thromboses and underwent a retransplantation. Mean peak aspartate amino transferase and amino alanine transferase levels were higher in patients in the histidine-tryptophan-ketoglutarate group (aspartate amino transferase, 661 ± 801 U/L; amino alanine transferase, 696 ± 964 U/L) than they were in patients in the University of Wisconsin group (aspartate amino transferase, 439 ± 415 U/L; amino alanine transferase, 464 ± 376 U/L); however, this difference was not significant. Mean total bilirubin, alkaline phosphatase, and gamma glutamyl transpeptidase levels, and international normalized ratios were similar in both groups.**

***Conclusions:*** **University of Wisconsin and histidine-tryptophan-ketoglutarate solutions are both effective in preserving live-donor liver allografts. In the current study, patients in the histidine-tryptophan-ketoglutarate group had higher peak aspartate amino transferase and amino alanine transferase levels initially, but these became almost identical by postoperative day 8.**

**Key words:** *Preservative solution, University of Wisconsin solution, Histidine-tryptophan-ketoglutarate solution, Living-donor liver transplantation*

Survival outcomes in liver transplantation have improved during the last 3 decades, and this has led to an increased demand for liver transplantation. Unfortunately, deceased-donor liver availability has remained relatively static, resulting in increased use of living donors for liver transplantation [1].

Hepatic allografts are rapidly cooled and then preserved in cold solutions prior to implantation. In deceased donor transplantation, grafts are initially preserved using Euro-Collins solution (SangStat, Lyon, France). The idea is to minimize cellular injury during cold preservation. The high potassium

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content of Euro-Collins solution prevents leakage of intracellular potassium and preserves intracellular function [2, 3]. However, in the late 1980s, the University of Wisconsin (UW) solution (Belzer, DuPont, Bad Homburg, Germany) was developed, which provides the nutrient substrate for the high-energy phosphate molecule, adenosine 5'-tri-phosphate (ATP), necessary for cellular metabolism. The UW solution also contains a buffering agent and an antioxidant. Using the UW solution led to an increase in cold preservation time in clinical practice that was observed both in US and in European studies, and

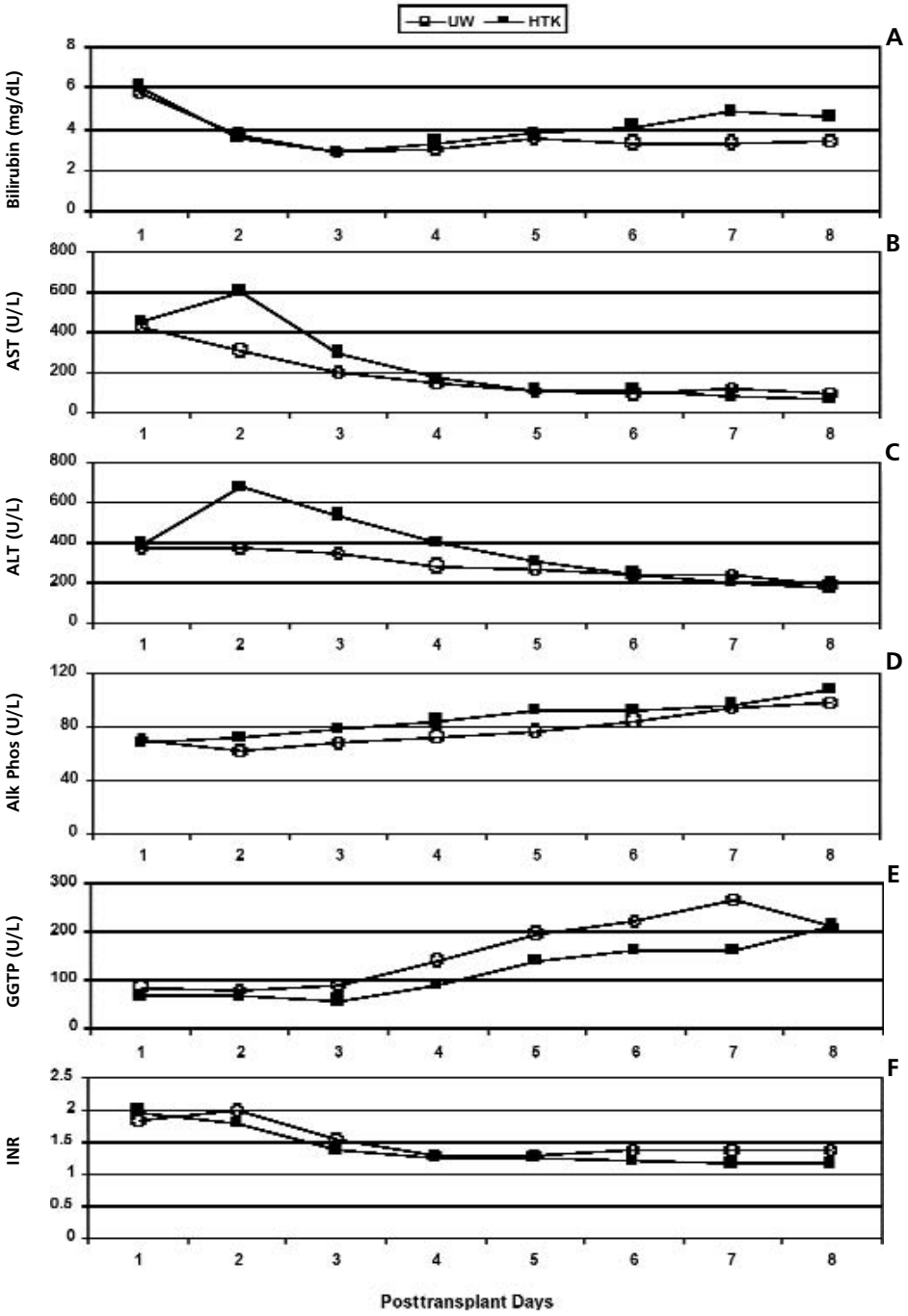


**Figure 1**. Mean total bilirubin (A), AST (B), ALT (C), alkaline phosphatase (D), GGTP (E) and INR (F) for first 8 postoperative days of graft either preserved in UW or HTK.

Bilirubin 1 mg/dL=17.1 μmol/L in SI units; AST, Aspartate amino transferase U/L; ALT, Amino alanine transferase U/L; $AlkPO_4$, Alkaline phosphatase U/L; GGTP, Gamma glutamyl transpeptidase U/L; INR, International normalized ratio

this development led to the transformation of liver transplantation from an emergency procedure to a semielective procedure. Both solutions have a high potassium content (Euro-Collins, 107; UW, 127 mmol/L) [4-7].

Histidine-tryptophan-ketoglutarate (HTK) solution (Dr. Köhler Chemie GmbH, Alsbach, Germany), which has a low potassium content, was initially used for cardioplegia of heart allografts. It also was used for cold preservation of liver allografts [8]. In deceased-donor liver transplantation, HTK solution has been reported as being as useful as UW solution [9-11]. Studies done to date comparing the 2 solutions have found them to be equally effective in preserving the liver allograft. Owing to the low potassium content in HTK solution, it is not mandatory to flush the allograft prior to reperfusion. Also, the HTK solution does not require additives, filtering, or premixing, and it is stable over a wide range of temperatures. It also is less viscous; hence, its flow is easy and rapid. HTK solution is increasingly being used for deceased donor liver transplantation [8, 10-13]. Such observations also have been published from researchers in Asian and European countries studying live-donor liver transplantation (LDLT) [11, 14]. However, literature from the United States about its effectiveness in preserving live-donor allografts is lacking. Therefore, we sought to examine the hepatic function of live-donor liver lobes preserved in UW solution compared with HTK solution after LDLT at our institution.

## Materials and Methods

Thirty-two adult-to-adult and 1 adult-to-child live-donor transplantations performed at our institution between July 2003 to August 2004 were included in this study. First, 9 allografts were perfused with cold UW solution, and then 24 allografts were perfused in cold HTK solution. The demographic characteristics of the 2 groups were compared (Table 1). Postoperative biochemical parameters including total bilirubin, aspartate amino transferase (AST), amino alanine transferase (ALT), alkaline phosphatase, gamma glutamyl transpeptidase (GGTP), and international normalized ratio (INR) were examined daily for the first 8 postoperative days and compared in both groups. Patients who required retransplantation for primary nonfunction were considered as having severe hepatic injury, while those with a total bilirubin level greater than 10 mg/dL (171 $\mu$mol/L) or an INR level greater than 2.0 by postoperative day 8 (in the absence of any obstructive anatomic complication) were considered as having hepatic dysfunction.

All donor hepatic resections and recipient implantations were performed by the same surgical team. A preoperative liver biopsy is routinely performed during evaluation of all potential donors at our center, and those with more than 10% steatosis are not accepted for LDLT liver donation. Donor hepatic resections were performed without the Pringle manoeuvre with preservation of inflow and outflow throughout the resection. Segments 5, 6, 7, and 8 were recovered in all cases, except in 2 donors in whom either segments 2 and 3 (for an adult-to-child transplant) or segments 2, 3, and 4 (for an adult-to-adult transplant) were recovered. The resections were done using unipolar diathermy (Valleylab, Boulder, Colo, USA), CUSA (Cavitronic Ultrasonic Aspirator) (Valleylab), Ligaclips (Weck Closure Systems, Research Triangle Park, NC, USA) Prolene sutures (Ethicon Inc, Somerville, NJ), and silk ties.

On the back table, grafts were perfused through the portal vein alone until the effluent fluid was clear. Care was taken to perfuse through major intrahepatic portal branches, and sutures and Ligaclips were removed from segment 5, segment 8, and short hepatic veins, if they needed to be implanted in the recipient (usually in veins > 5 mm). This was done to ensure perfusion of all the segments without discoloration. To avoid intimal damage, the hepatic artery was not perfused with the preservative solution. After flushing, the same solution was used for preservation. For each patient in the UW group, a total of 3 liters of UW was used for flushing; the first 2 liters of effluent was discarded, and last liter was used to preserve the graft until implantation. Similarly, 5 liters of HTK was used for flushing the graft for each patient in the other group. The first 4 liters of effluent was discarded, and last liter was used to preserve the graft until implantation.

The recipient surgery was performed in piggy-back fashion without veno-venous bypass. The right hepatic vein of the donor was sutured to the right hepatic vein of the recipient using a cavaplasty technique (except in 2 patients in whom the left hepatic segments were used). A portal vein anastomosis was performed either with the recipient right portal vein or with the main portal vein. A hepatic arterial anastomosis was performed under a microscope (at 10X power) after portal perfusion of the

allograft. Additional venous drainage of the short hepatic veins was performed before portal perfusion. Segment-5 and/or segment-8 veins were drained after portal perfusion when necessary.

All patients were started on a triple immunosuppression medication regimen consisting of oral tacrolimus (3 mg PO, b.i.d., with a target trough level of 8-10 ng/mL), intravenous mycophenolate mofetil (MMF) (1 g, b.i.d.) and steroid (methyl prednisolone, 500 mg before hepatic perfusion then 100 mg twice a day on day1, 80 mg twice a day on day 2, 60 mg twice a day on day 3, 40 mg twice a day on day 4, and 20 mg twice a day on day 5). The donor and recipient characteristics, primary diagnosis, model for end-stage liver disease score, and graft-to-recipient weight ratio are given in Table 1.

**Table 1.** Demographics and diagnoses

| | UW (n = 9) | HTK (n = 24) |
|---|---|---|
| **Donor** | | |
| Age (y) | 37.7 ± 6.8 | 38.8 ± 10.5 |
| Male/female | 4/5 | 10/14 |
| Graft weight (g) | 717.5 ± 187.4 | 874.8 ± 173.5 |
| Ischemia time (min) | 54.7 ± 23.4 | 48.6 ± 28.9 |
| **Recipient** | | |
| Age (y) | 47.3 ± 20.2 | 50.6 ± 11.5 |
| Male/female | 3/6 | 16/8 |
| Weight (kg) | 63.9 ± 21.8 | 81.3 ± 16.9 |
| Graft/weight ratio | 1.2 ± 0.7 | 1.1 ± 0.3 |
| MELD score | 14.9 ± 4.3 | 13.7 ± 4.9 |
| **Diagnosis** | | |
| ETOH | 2 | 3 |
| HCV | 0 | 2 |
| HCV with HCC | 1 | 2 |
| HBV | 0 | 1 |
| PBC | 2 | 4 |
| PSC | 0 | 5 |
| Hemochromatosis | 1 | 1 |
| Autoimmune | 1 | 1 |
| Cryptogenic | 1 | 4 |
| Cryptogenic with HCC | 0 | 1 |
| OTC Deficiency | 1 | 0 |

UW, University of Wisconsin solution; HTK, Histidine-tryptophan-ketoglutarate solution; ETOH, Ethanol abuse; HCV, Hepatitis C viral infection; HBV, Hepatitis B viral infection; HCC, Hepatocellular carcinoma; PBC, Primary biliary cirrhosis; PSC, Primary sclerosing cholangitis; OTC, Ornithine transcarbamylase; MELD, Model for end-stage liver disease

### *Statistical analyses*

Data are presented as means ± standard deviation. Means are compared using the Student *t* test, with a value for *P* less than .05 considered significant. SPSS software (Statistical Package for the Social Sciences, version 13.0, SSPS Inc, Chicago, Ill, USA) was used for all statistical analyses.

## Results

### *Survival*

All patients were alive at the end of the study. None of the patients in either group had primary nonfunction of the graft that required retransplantation. Two patients in the HTK group experienced an early hepatic artery thrombosis that required retransplantation. These patients were excluded from the analysis. No patient in the UW group experienced a hepatic artery thrombosis.

### *Hepatic function*

Levels for mean total bilirubin, AST, ALT, alkaline phosphatase, GGTP, and INR during the first 8 postoperative days for both groups are shown in Figures 1 A, B, C, D, E, and F. Overall peak AST and ALT were higher patients in the HTK group (AST, 545 ± 696 U/L; ALT, 532 ± 682 U/L) than they were in patients in the UW group (AST, 440 ± 415 U/L; ALT, 364 ± 370 U/L), although the difference was not significant. At postoperative day 8, these values were almost identical. Mean peak levels for total bilirubin, alkaline phosphatase, GGTP, and INR were similar in both groups and are shown in Table 2.

Four patients in the UW group and 10 patients in the HTK group had graft weight ratios less than or equal to 1.0, and 5 patients in the UW and 14 patients in the HTK group had graft weight ratios greater than 1.0. When the 2 groups' peak biochemical parameters within the first 8 postoperative days were compared in relationship to graft weight ratio, no significant differences were observed (Table 2).

**Table 2.** Mean peak values of biochemical parameters

| Mean Peak value | | *n* | T Bili | *p* | AST | *p* | ALT | *p* | Alk $PO_4$ | *p* | GGTP | *p* | PT (INR) | *P* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Overall** | **UW** | 9 | 111.2 ± 53.0 | .865 | 439 ± 415 | .675 | 464 ± 376 | .781 | 103 ± 39 | .700 | 222 ± 161 | .369 | 2.2 ± 0.5 | .449 |
| | **HTK** | 22 | 116.3 ± 63.3 | | 545 ± 696 | | 532 ± 682 | | 112 ± 67 | | 173 ± 124 | | 2.0 ± 0.4 | |
| **Graft weight** | **UW** | 4 | 126.5 ± 75.2 | .364 | 278 ± 94 | .472 | 234 ± 59 | .350 | 88 ± 44 | .776 | 182 ± 108 | .964 | 2.1 ± 0.2 | .893 |
| **ratio ≤ 1** | **HTK** | 10 | 85.5 ± 27.4 | | 377 ± 255 | | 372 ± 275 | | 83 ± 24 | | 179 ± 123 | | 2.1 ± 0.2 | |
| **Graft weight** | **UW** | 5 | 99.2 ± 34.2 | .263 | 568 ± 539 | .795 | 648 ± 430 | .968 | 115 ± 35 | .574 | 254 ± 200 | .307 | 2.0 ± 0.7 | .945 |
| **ratio > 1** | **HTK** | 12 | 139.4 ± 73.5 | | 685 ± 908 | | 665 ± 885 | | 137 ± 81 | | 168 ± 130 | | 2.0 ± 0.5 | |

UW, University of Wisconsin solution; HTK, Histidine-tryptophan-ketoglutarate solution; T Bili, Total bilirubin μmol/L (17.1 μmol/L = 1mg/dL); AST, Aspartate amino transferase U/L; ALT, Amino alanine transferase U/L; $AlkPO_4$, Alkaline phosphatase U/L; GGTP, Gamma glutamyl transpeptidase U/L; INR, International normalized ratio

*Hepatic dysfunction*

One patient in the UW group (patient No. 5) and 2 patients in the HTK group (patient Nos. 31 and 33) had an elevated total bilirubin level of more than 171 μmol/L on postoperative day 8. Also, 1 patient in the UW group (again, patient No. 5) had an INR greater than 2.0, and 1 patient (patient No. 25) in the HTK group had an INR greater than 2.0 on postoperative day 8. Their graft weight ratio and peak biochemical abnormalities are shown in Table 3.

## Discussion

Initially, deceased donor allografts were perfused with Euro-Collins solution, which has a high potassium content, and allografts could be preserved safely for 6 to 8 hours. However, while the Euro-Collins solution only preserved intracellular leakage and provided a buffering agent, UW solution provided, in addition, the substrate for formation of a high-energy molecule, ATP. Depletion of ATP is thought to be the main reason for cellular injury during cold ischemia and reperfusion [9]. With the availability of the UW solution, liver allografts could be preserved safely beyond 16 hours, as demonstrated by the extended preservation times reported by Belzer group and others [4-7].

Furukawa and colleagues have shown successful preservation of deceased donor allografts up to 36 hours using UW solution [15]. However, the risk of hepatic dysfunction increases progressively with increases in cold ischemia times beyond 16 hours. In these authors' series, some patients were initially perfused either with cold Ringer's solution or Euro-Collins solution, and the final perfusion and preservation were done using UW solution to save on the cost of organ recovery. Nevertheless, prolonged, safe cold storage time with UW solution has been uniformly reported by many studies [4, 16-18]. Addition of the substrate for ATP results in better and longer preservation times, with reduced rates of primary nonfunction and allograft dysfunction. UW solution, therefore, has been universally accepted and used for perfusion and preservation of liver allografts.

Other solutions like Marshall's, Newcastle, and Celsior have been available [19-23], but UW remains the gold standard at most transplant centers.

However, both Euro-Collins and UW have a high potassium content; hence, organs must be perfused with potassium-free cold solution just before reperfusion. HTK solution was formulated in Germany by Bretschneider (1980) and was initially used for cardioplegia and subsequently for cold preservation of other organs [24]. Histidine in HTK solution reduces acidosis, tryptophan prevents membrane injury, and ketoglutarate provides the substrate for high-energy bonds. HTK solution, with less potassium content and less viscosity, flows easily with gravity, perfuses the liver rapidly, and obliterates the need for washing the preservative solution from the allograft just before reperfusion. However, at our center, we have elected to perfuse with cold Ringer's solution just prior to reperfusion of the allograft. Ringer's lactate solution would have the same advantage as far as ease of use; however, it would lack the preservative substrate for high-energy molecule present in HTK required to better preserve hepatocytes in cold storage. Upadhyay and coauthors have predicted the superiority of UW and HTK over Euro-Collins because both UW and HTK preserve matrix metalloproteinases, whereas Euro-Collins is ineffective in preserving matrix metalloproteinases [25, 26]. From our observations, UW and HTK are both useful in perfusing and preserving live-donor liver allografts and in preventing primary nonfunction. One remarkable difference we observed was that higher AST and ALT levels were found in patients in the HTK group compared with those in the UW group. This difference narrowed quickly, however, as these values were nearly identical by the end of the eighth postoperative day. The Kyoto group found better oxygen saturation of hemoglobin in hepatic tissue with use of HTK solution compared with the UW; they also reported lower

**Table 3.** Biochemical abnormalities in patients with hepatic dysfunction

| Patient No. | Graft weight ratio | T bili | | AST | | ALT | | $AlkPO_4$ | | GGTP | | INR | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Day 8 | Peak | Day 8 | Peak | Day 8 | Peak | Day 8 | Peak | Day 8 | Peak | Day 8 | Peak |
| 5 UW | .75 | 191.5 | 206.9 | 106 | 346 | 151 | 264 | 52 | 64 | 167 | 168 | 2.2 | 2.8 |
| 25 HTK | .70 | 107.7 | 119.7 | 64 | 265 | 150 | 251 | 66 | 69 | NA | 105 | 2.3 | 2.3 |
| 31 HTK | 1.06 | 251.4 | 271.9 | 34 | 296 | 59 | 346 | 144 | 144 | 131 | 131 | 0.9 | 1.7 |
| 33 HTK | 198.4 | 11.6 | 56.4 | 49 | 200 | 190 | 374 | 227 | 227 | NA | 131 | 1.4 | 1.6 |

T Bili, Total bilirubin μmol/L(17.1 μmol/L = 1mg/dL); AST, Aspartate amino transferase U/L; ALT, Amino alanine transferase U/L; $AlkPO_4$, Alkaline phosphatase U/L; GGTP, Gamma glutamyl transpeptidase U/L; INR, International normalized ratio; NA, Not available

AST levels when using HTK compared with UW in the allografts [12].

Higher AST and ALT levels during the early postoperative period when using the HTK solution, with no subsequent clinical consequences, are somewhat surprising and difficult to explain. Nonetheless, this also has been observed in Germany [11]. Lange and coworkers studied hepatic enzyme activity in the effluent fluid from back table flush and found that the enzyme activity in HTK-preserved allografts was higher compared with that preserved in UW solution; however, this difference was not significant [14]. Also, Janssen and coworkers, in human liver endothelial cell tube models, showed that loss of cell viability was significantly reduced after ischemia and reperfusion when the HTK solution was used as compared with when the UW solution was used [9]. These observations somewhat agree with our observations and observations from other studies from Europe [11].

However, contrary observations have been reported by Hatano and coworkers. These authors reported higher oxygen saturation and better perfusion heterogeneity in HTK-preserved allografts, when compared with allografts preserved in UW solution, as measured by infrared spectrometry. Similar observations have been reported in LDLT by Vine and colleagues [27, 28].

In the current report, 2 patients developed hepatic artery thrombosis in the HTK group; we believe these to be incidental. We do not believe that hepatic artery thrombosis could be attributed to the preservative solution used, but that it occurred because of the smaller size of the artery, despite microvascular anastomosis under 10 × magnification. In our observation, the rates of hepatic dysfunction in the UW and HTK groups were comparable. Also, the peak values of each biochemical parameter, indicative of hepatic function for graft weight ratio less than or equal to 1 or greater than 1, were comparable and did not reach statistical significance, although the trend was toward higher AST and ALT levels with the use of HTK solution.

## Conclusions

As observed in deceased donor liver transplantation, our observations confirm that both UW and HTK are satisfactory solutions for preserving live-donor liver allografts. There were no cases of primary nonfunction, and the hepatic dysfunction rate was 12%. HTK-preserved allografts had higher peak transaminase levels without clinical consequences. More prospective, controlled, randomized studies with larger populations are required to determine whether any differences exist between these preservative solutions.

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