## ORIGINAL ARTICLE

# Comparative Prospective Study of Two Liver Graft Preservation Solutions: University of Wisconsin and Celsior

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University of Wisconsin solution (UWS) is the gold standard for graft preservation. Celsior solution (CS) is a new solution not as yet widely used in liver grafts. The aim of this study was to compare the liver function of transplanted grafts stored in these 2 preservation solutions. The primary endpoints were the rates of primary nonfunction (PNF) and primary dysfunction (PDF). We performed a prospective and pseudorandomized study that included 196 patients (representing 104 and 92 livers preserved in UWS and CS, respectively) at La Fe University Hospital (Valencia, Spain) between March 2003 and May 2005. PNF and PDF rates, liver function laboratory parameters, postoperative bleeding, vascular and biliary complications, and patient and graft survival at 3 years were compared for the 2 groups. The 2 groups were similar in terms of donor variables, recipient variables, and surgical techniques. The PNF rates were 2.2% and 1.9% in the CS and UWS groups, respectively ($P =$ not significant), and the PDF rates were 15.2% and 15.5% in the CS and UWS groups, respectively ($P =$ not significant). There were no significant differences in the laboratory parameters for the 2 groups, except for alanine aminotransferase levels in month 3, which were lower in the CS group ($P = 0.01$). No significant differences were observed in terms of complications. Three-year patient and graft survival rates were as follows for years 1, 2, and 3: 83%, 80%, and 76% (patient) and 80%, 77%, and 73% (graft) for the UWS group and 83%, 77%, and 70% (patient) and 81%, 73%, and 67% (graft) for the CS group ($P =$ not significant). In conclusion, this study shows that CS is as effective as UWS in liver preservation. *Liver Transpl 15: 1709-1717, 2009.* © 2009 AASLD.

Since liver transplantation requirements were established as we know them today, the National Institutes of Health Consensus Development Conference (Bethesda, MD)[1] has implemented important changes in surgical techniques, donor and recipient selection criteria, and preoperative and postoperative patient management. However, since University of Wisconsin solution (UWS) was developed 20 years ago, progress in terms of liver preservation solutions has been limited.[2]

The final outcome of transplantation is closely linked to graft quality, which, in turn, is determined by factors such as donor age and diseases, donor maintenance until harvest, the cold ischemia time, and the methods used to protect the organ from ischemia-reperfusion injury.[3,4]

Preservation techniques are essential for keeping organs viable outside the body until transplantation, so the perfection of preservation solution components ultimately helps to improve transplantation outcomes.

Ischemic preservation injury negatively affects graft dysfunction. Several graft-related molecules have been shown to correlate with early graft dysfunction and poor outcome in the immediate postoperative period.[5,6] The mechanisms that underlie both primary nonfunction (PNF) and primary dysfunction (PDF) are not entirely understood, but they most likely involve isch-

emia-reperfusion injury, which develops soon after transplantation and greatly depends on conditions during organ harvesting, organ preservation, and recipient health.[7] UWS has been the gold standard for liver preservation since 1987, replacing the previously widely used Euro-Collins solution (Fresenius AG, Bad Homburg, Germany).[8]

Celsior solution (CS; Genzyme Corp., Naarden, the Netherlands), a preservation solution that has recently become available, may offer new prospects for improving graft preservation quality and transplantation outcomes.[9]

Specifically designed for heart preservation, CS is a high-sodium, low-potassium extracellular low-viscosity solution with a formulation aimed at preventing cell swelling (mannitol and lactobionate), oxygen-derived free radical injury (reduced glutathione, histidine, and mannitol), and contracture by means of enhanced energy production (glutamate) and limited calcium overload (a high magnesium content and a slight degree of acidosis).[9] The theoretical advantages of CS over UWS include more rapid organ flushing because of its lower viscosity and higher buffering capacity. The efficacy of CS in kidney and liver preservation has already been established in animal models.[10-12] CS has recently been used with good clinical results in the preservation of abdominal grafts, although the experience with liver transplantation is still limited.[13,14] Only a few small studies have been published on the clinical use of CS.[15-20]

Our study was a prospective, pseudorandomized, single-center pilot study in humans designed to determine the efficacy of CS compared to UWS as a preservation solution for liver allografts.

To demonstrate our main hypothesis that CS is efficacious in graft preservation for liver transplantation, we compared the efficacy of CS to that of UWS, which is considered to be the gold-standard solution.

The primary endpoints were the PNF and PDF values for liver grafts in both series, as defined by Ploeg et al.[4]

Secondary endpoints, including postoperative bleeding, vascular and biliary complications, and patient and graft actuarial survival for up to 3 years post-transplantation, were also compared for both groups.

## PATIENTS AND METHODS

We designed an open-label, comparative, prospective, pseudorandomized study to assess the outcome of liver graft preservation using UWS and CS in orthotopic liver transplantation.

This study was conducted in accordance with the principles of the ICH Harmonized Tripartite Guidelines for Good Clinical Practice and the Declaration of Helsinki. It was approved by the hospital ethics and research board, and all included patients gave their prior informed consent.

### Inclusion Criteria

The study included all whole liver transplants from cadaveric donors targeted for use in primary and single liver transplants in adult recipients (18 years old and older).

### Exclusion Criteria

Exclusion criteria were reduced-size split grafts, live-donor grafts, non–heart-beating donors, liver retransplants, domino liver transplants, pediatric recipients, acute liver failure as the etiology for transplantation, multiorgan recipients, and grafts procured by other surgical teams.

### Sample Size

The sample size was determined with the assumption of a PNF plus PDF rate of 10%, which was based on our previous results. A total of 97 patients were required in order to detect a 15% difference in the PNF plus PDF rate between the 2 study groups for a significance level of 0.05 and a statistical power of 80%.

Two medical teams participated in liver harvesting. Each team used the same preservation solution for 3 consecutive livers and then switched to the other solution for the 3 next livers. The team for each harvest was randomly appointed whenever a suitable donor became available.

### Technical and Immunosuppression Aspects

The Starzl surgical technique[21] was used for liver harvesting. Livers were perfused in situ, with approximately 2 liters of solution, through the aorta and portal vein at a gravity-hydrostatic pressure of 75 to 100 cm $H_2O$ at 4°C. The first liter was rapidly infused, and the second was perfused slowly until the procedure was complete. Perfusion continued until the solution drained clean and free of blood through the suprahepatic inferior vena cava. The total perfusion volume and duration were decided by each surgical team according to the manufacturer's indications and previous clinical experience. The organ was submerged for transfer in the same preservation solution used for perfusion and was kept at 4°C during storage and back-table preparation. The aorta and portal vein were not perfused with additional solution during back-table preparation.

The surgical technique preserved the recipient's vena cava (piggyback technique) without a bypass or temporary portal-caval anastomosis.

The hospital protocol included double immunosuppressive therapy with cyclosporine or tacrolimus plus steroids, except for patients with kidney failure or insulin-dependent diabetes, and triple therapy with azathioprine for autoimmune cirrhosis.

### Data Collection

The liver function of the transplanted grafts was assessed by a comparative analysis of laboratory parameters [aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, and prothrombin time] on days 1, 3, 7, 15, and 30 and at 3 and 12 months post-transplantation.

| TABLE 1. Donor Variables | | | |
|---|---|---|---|
| | CS (n = 92) | UWS (n = 104) | P |
| Gender (male/female) | 57 (62%)/35 (38%) | 53 (51%)/51 (49%) | 0.12 |
| Age (years) | 54.3 (15–82) | 51.4 (14–82) | 0.22 |
| Cause of death [n (%)] | | | 0.46 |
|   Cerebrovascular | 68 (73.9) | 70 (67.3) | |
|   Trauma | 15 (16.3) | 21 (20.2) | |
|   Other | 9 (9.8) | 13 (12.5) | |
| Inotropic drugs [n (%)] | | | 0.79 |
|   No | 39 (42.4) | 46 (44.3) | |
|   Yes | 53 (57.6) | 58 (55.7) | |
| Hypotension episodes [n (%)] | | | 0.08 |
|   0 | 65 (70.7) | 60 (57.7) | |
|   1 | 24 (26.1) | 42 (40.4) | |
|   2 | 1 (1.1) | 2 (1.9) | |
|   3 | 2 (2.2) | 0 (0) | |
| AST (U/L) | 38 (9–261) | 43 (11–400) | 0.49 |
| ALT (U/L) | 40.4 (8–304) | 43.3 (5–414) | 0.44 |
| Total bilirubin (mg/dL) | 0.78 (0.1–3.5) | 0.7 (0.1–5.4) | 0.96 |
| APTT (%) | 71.3 (20–112) | 72.5 (14–100) | 0.76 |
| Sodium (mEq/L) | 147.4 (124–169) | 148.8 (126–182) | 0.38 |
| Perfusate volume (mL) | 4464 ± 590 | 4440 ± 620 | 0.02 |
| Steatosis (n) | | | 0.79 |
|   None/mild (<30%) | 90 (97.8) | 103 (99) | |
|   Moderate (30%-60%) | 2 (2.2) | 1 (1) | |

**Abbreviations:** ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; CS, Celsior solution; UWS, University of Wisconsin solution.

## Statistical Analysis

### Descriptive Statistics

In the case of quantitative variables, a descriptive analysis was performed of the characteristics of the groups according to the preservation solution used. The mean value was calculated as the distribution midpoint for variables showing a normal or Gaussian distribution. The nonsymmetrical statistical variables were the medians, confidence intervals, maximum values, and minimum values. Because most of the variables did not comply with normality criteria, they were compared with the nonparametric Mann-Whitney U test.

The qualitative variables for both groups were described in frequency distribution tables (frequency and percentage). Distribution homogeneity was compared with the chi-square test.

### Comparative Statistics

To compare trends for the liver function parameters, a repeated-measure analysis of variance was performed to verify any changes in parameter trends and to determine whether any parameter varied according to the preservation solution used.

To analyze patient and graft survival, a survival analysis was performed by the adjustment of the Kaplan-Meier curve to the number of weeks post-transplantation up to the recipient's death or graft loss and by the comparison of the curves according to the preservation solution with the log-rank test with a significance level of 0.05.

## RESULTS

Between March 2003 and May 2005, 232 liver transplants were performed at La Fe University Hospital. Either UWS or CS was used as the preservation solution. A total of 196 transplant patients were included in the study, 104 and 92 of whom were transplanted with livers preserved in UWS and CS, respectively. The remaining 36 cases were rejected because requirements were not met: 14 had retransplants, 10 were pediatric cases, 9 were patients with transplants performed by other transplantation units, and 3 underwent combined transplantation. One death occurred during the surgical procedure in the group of patients with livers preserved in UWS.

### Donor and Recipient Characteristics

The main donor characteristics for the 2 groups are summarized in Table 1. No significant differences were observed between the 2 study groups in terms of age, gender, number of hypotension episodes, cause of donor death, use of vasoactive drugs for maintenance in the intensive care unit, degree of hepatic steatosis, sodium values, or total bilirubin, AST, ALT, and prothrombin time values.

Recipient demographic and clinical characteristics are summarized in Table 2. Patients were uniformly distributed in the 2 groups with respect to age, gender, liver transplantation indication (including etiology), and Child-Pugh class at the time of transplantation. The proportion of recipients with hepatitis C

| TABLE 2. Recipient Variables | | | | | |
|---|---|---|---|---|---|
| | CS (n = 92) | | UWS (n = 104) | | |
| | n | % | n | % | P |
| Gender (men/women) | 75/17 | 81.5/18.5 | 76/28 | 73.1/26.9 | 0.16 |
| Age (years) | | 53.1 (37–66) | | 52.9 (19–67) | 0.85 |
| Diagnosis | | | | | |
|   Viral postnecrotic cirrhosis | | | | | 0.34 |
|     No | 32 | 34.8 | 43 | 41.3 | |
|     Yes | 60 | 65.2 | 61 | 58.7 | |
|   Ethanol-related postnecrotic cirrhosis | | | | | 0.47 |
|     No | 52 | 56.5 | 64 | 61.5 | |
|     Yes | 40 | 43.5 | 40 | 38.5 | |
|   Hepatocarcinoma | | | | | 0.27 |
|     No | 55 | 59.8 | 70 | 67.3 | |
|     Yes | 37 | 40.2 | 34 | 32.7 | |
|   Cholestatic cirrhosis | 4 | 4.3 | 5 | 4.8 | |
|   No cirrhosis | 3 | 3.3 | 3 | 2.9 | |
| Child's class | | | | | 0.96 |
|   NA | 3 | 3.3 | 3 | 2.9 | |
|   A | 12 | 13 | 14 | 13.5 | |
|   B | 32 | 34.8 | 33 | 31.7 | |
|   C | 45 | 48.9 | 54 | 51.9 | |
| Blood group | | | | | 0.85 |
|   O | 43 | 46.7 | 43 | 41.3 | |
|   A | 37 | 40.2 | 46 | 44.2 | |
|   B | 10 | 10.8 | 12 | 11.5 | |
|   AB | 2 | 2.2 | 3 | 2.9 | |

**Abbreviations:** CS, Celsior solution; NA, not applicable-patients not cirrhotic; UWS, University of Wisconsin solution.

| TABLE 3.  Technical Aspects | | | |
|---|---|---|---|
| | CS (n = 92) | UWS (n = 104) | P |
| Hepatectomy [n (%)] | | | 0.40 |
|   Classic | 0 (0) | 2 (1.9) | |
|   Piggyback | 92 (100) | 102 (98.1) | |
| Cold ischemia time (minutes) | 323.93 (150–580) | 361.75 (160–680) | 0.76 |
| Warm ischemia time (minutes) | 44.64 (25–70) | 43.75 (20–85) | 0.12 |
| Artery delay (minutes) | 43.93 (25–60) | 38 (0–80) | 0.21 |
| Total ischemia time (minutes) | 368.57 (195–615) | 405.50 (185–730) | 0.56 |
| RBC transfusion (units) | 2.64 (0–8) | 2.75 (0–8) | 0.47 |
| Platelet transfusion (units) | 1.57 (0–2) | 1.55 (0–4) | 0.40 |
| Plasma transfusion (units) | 2.43 (0–4) | 2.75 (0–8) | 0.31 |
| Blood autotransfusion (mL) | 531.07 (0–1220) | 600.60 (0–1900) | 0.94 |
| Liver congestion [n (%)] | | | 0.53 |
|   None/mild | 65 (78.7) | 74 (71.2) | |
|   Moderate | 22 (23.9) | 28 (26.9) | |
|   Severe | 5 (5.4) | 2 (1.9) | |
| Surgical time (minutes) | 256.07 (190–315) | 255 (175–390) | 0.56 |

**Abbreviations:** CS, Celsior solution; RBC, red blood cell; UWS, University of Wisconsin solution.

virus was 51% in the UWS series and 58.7% in the CS series.

No significant differences were observed in the ischemia time, hepatectomy technique, blood transfusions, surgical time, or artery delay (the interval in minutes between portal reperfusion and hepatic artery reperfusion), among other factors (Table 3).

The results for posttransplantation variable analysis are summarized in Table 4. The perfusate volume was higher in the CS group than in the UWS group: the mean CS volume was 4464 ± 590 mL (median, 4250 mL) versus a mean UWS volume of 4440 ± 620 mL (median, 4000 mL). These differences were statistically significant (*P* = 0.02), although the differences in the

| TABLE 4. Clinical Outcomes | | | |
|---|---|---|---|
| | CS (n = 92) | UWS (n = 103) | P |
| Intensive care unit stay (days) | 5.33 (1–49) | 6.07 (1–56) | 0.09 |
| Liver graft function [n (%)] | | | 0.11 |
| Normal | 76 (82.6) | 85 (82.5) | |
| Primary dysfunction | 14 (15.2) | 16 (15.5) | |
| Primary nonfunction | 2 (2.2) | 2 (1.9) | |
| Postoperative complication [n (%)] | | | |
| Bleeding | 10 (11) | 9 (8.7) | 0.83 |
| Arterial | | | 0.84 |
| Thrombosis | 3 (3.3) | 2 (1.9) | |
| Stenosis | 1 (1.1) | 1 (0.9) | |
| Venous | | | 0.36 |
| Portal thrombosis | 0 (0) | 1 (0.9) | |
| Hepatic thrombosis | 1 (1.1) | 0 (0) | |
| Biliary | | | 0.63 |
| Leak | 9 (9.7) | 9 (8.7) | |
| Stenosis | 2 (2.2) | 4 (3.9) | |
| Other | 5 (5.4) | 9 (8.7) | |

**Abbreviations:** CS, Celsior solution; UWS, University of Wisconsin solution.

volumes were quite small, and we do not consider them clinically relevant because the mean values were quite similar.

Stay in the posttransplantation intensive care recovery unit tended to be longer for patients in the UWS group ($P = 0.09$), with a mean stay of 6.07 days (median, 4 days) versus 5.33 days (median, 3 days) for the CS group.

The initial graft function was largely satisfactory in both study groups, with 76 cases in the CS group (82.6%), and 85 cases in the UWS group (82.5%). In the CS group, 14 cases of PDF (15.2%) and 2 cases of PNF (2.2%) were diagnosed versus 16 cases (15.5%) and 2 cases (1.9%), respectively, in the UWS group. No significant differences ($P = 0.83$) were observed in terms of distribution according to the preservation solution.

Cytolysis, cholestasia, and clotting factor synthesis parameters were also compared for the 2 groups in the immediate postoperative period and over the first year of follow-up.

A comparison of mean and median AST levels at days 1, 3, 7, 15, 30, 90, and 365 post-transplantation showed no significant differences between the 2 groups. The distribution of the marginal means for different time periods for both groups is shown in Fig. 1A. In the third posttransplantation month, significant differences ($P = 0.01$) were observed in the mean ALT levels between the groups, with the lowest mean ALT level observed in the CS group with a mean of 71 U/L (range, 10-519) versus a mean of 96 U/L (range, 8-559) for the UWS group. No significant differences were found in the ALT levels in the other periods (Fig. 1B), nor were significant differences observed in a comparison of the mean values for the total bilirubin and prothrombin time (Fig. 1C,D).

Another study objective was to compare postoperative bleeding and arterial, venous, and biliary complications in the 2 groups (Table 4). No significant differences were found in a comparison of the distribution of the various complications according to the preservation solution used.

Biliary leakage in the UWS group occurred in biliary anastomoses in 6 patients and after T-tube removal in 3 patients; the corresponding numbers of cases for the CS groups were 5 and 4. Leaks were treated conservatively and with radiology techniques; no relaparotomy was performed. Biliary stenosis was diagnosed in anastomoses in 3 cases with UWS. One case involved an ischemic-type biliary lesion resulting from an arterial complication that made retransplant necessary. Dilatation was sufficient in 2 of the patients, and a hepaticojejunostomy technique had to be used for 1 patient. In the CS series, there were 2 anastomosis stenoses, 1 of which required a hepaticojejunostomy. Other biliary complications were choledocholithiasis, oddities, and poorly positioned T-tubes.

The mean patient follow-up time was 25.9 ± 12.5 months, and the median was 29 months (range, 0-46 months). Actuarial survival for the first year was 83% in both groups. At 2 and 3 years, actuarial survival was 80% and 76% in the UWS group, respectively, and 77% and 70% in the CS group, respectively. These differences were not statistically significant.

Reasons for patient death in the UWS group were sepsis (8 cases), pneumonia (3 cases), respiratory failure (2 cases), acute renal failure (3 cases), multiorgan failure (1 case), acute pancreatitis (1 case), primary liver nonfunction (1 case), massive hemothorax (1 case), cerebrovascular stroke (1 case), bone metastases (1 case), and intraoperative death after severe reperfusion syndrome (1 case). Reasons for patient death in the CS group were pneumonia (7 cases), sepsis (7 cases), hepatic coma (2 cases), bone metastases (2 cases), gastrointestinal bleeding (1 case), cerebral bleeding (1
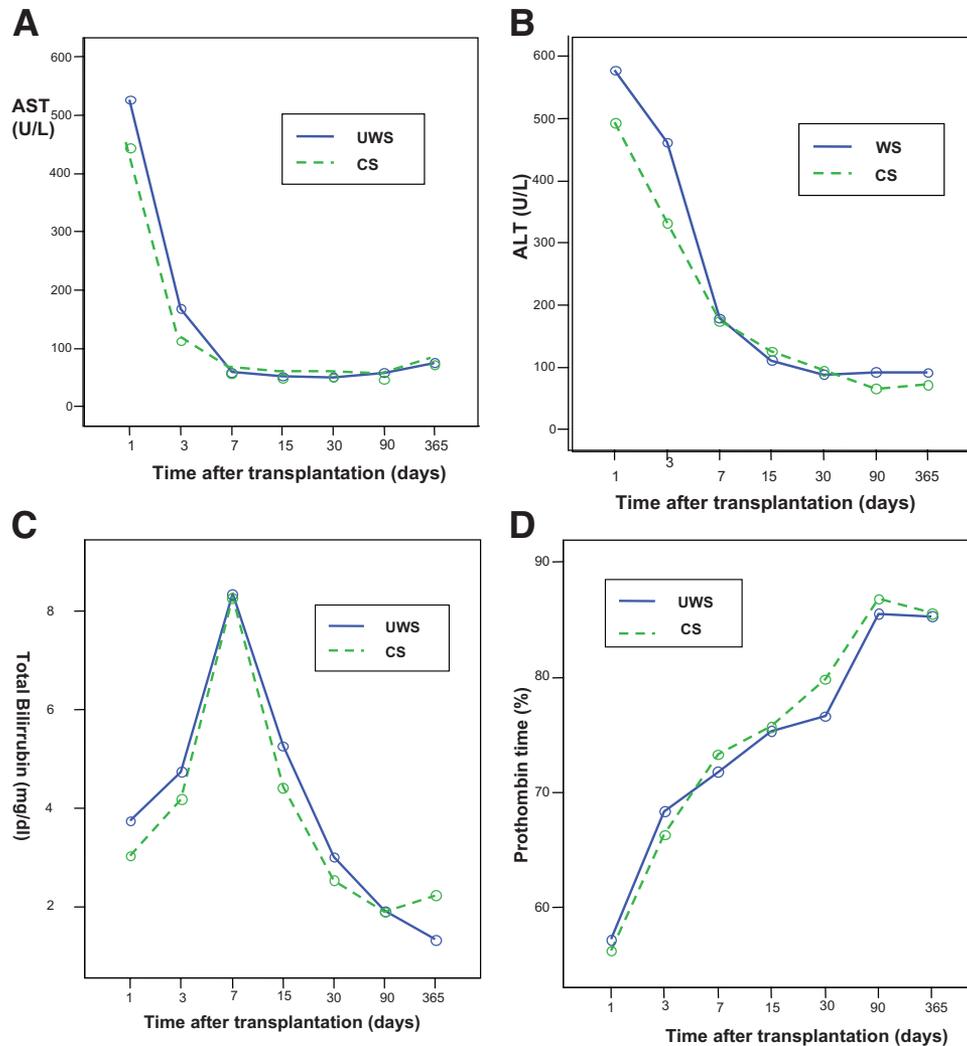
**Figure 1.** Comparison of the cytolysis, cholestasia, and synthesis analytical parameters after liver transplantation: (A) mean AST, (B) mean ALT, (C) mean total bilirubin, and (D) mean prothrombin time (%). Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CS, Celsior solution; UWS, University of Wisconsin solution.

case), chronic rejection (1 case), cardiac arrest (1 case), hydropic decompensation (1 case), and acute renal failure (1 case).

The mean graft follow-up was 25.1 ± 12.7 months, and the median was 28 months (range, 0-46 months). Actuarial survival rates for years 1, 2, and 3 were 80%, 77%, and 73%, respectively, for the UWS group, and 81%, 73%, and 67%, respectively, for the CS group. No significant differences in graft survival were observed when we compared distributions according to the preservation solution used.

There were 3 graft failures with retransplant cases in the UWS group: 1 PNF case and 2 cases of subsequent nonfunction (months 9 and 10) due to arterial thrombosis and chronic rejection. In the CS group, there were 4 graft failures with retransplant cases: 2 PNF cases and 2 cases of subsequent nonfunction (months 9 and 22) due to Budd-Chiari syndrome and artery thrombosis. Patient and graft survival results are shown in Fig. 2.

## DISCUSSION

Liver transplantation is a successful treatment for patients with chronic terminal liver disease. Although the number of transplants performed annually is increasing, the number of candidates placed on waiting lists is increasing even more, and this has resulted in a growing waiting-list mortality rate. Sociodemographic changes in our society have led to changes in both donor and recipient characteristics resulting largely from improved life expectancy and an associated higher prevalence of chronic conditions.

The greater demand for grafts has led to changes in the criteria for accepting cadaveric donor livers for implantation. Nowadays, the number of older, suboptimal, and nonideal donors (eg, those with longer stays in the organ generator unit, those with comorbidities, those treated with higher dosages of catecholamine vasoconstrictors, and those with higher levels of steatosis) is increasing.[22] The definition of a suboptimal or mar-
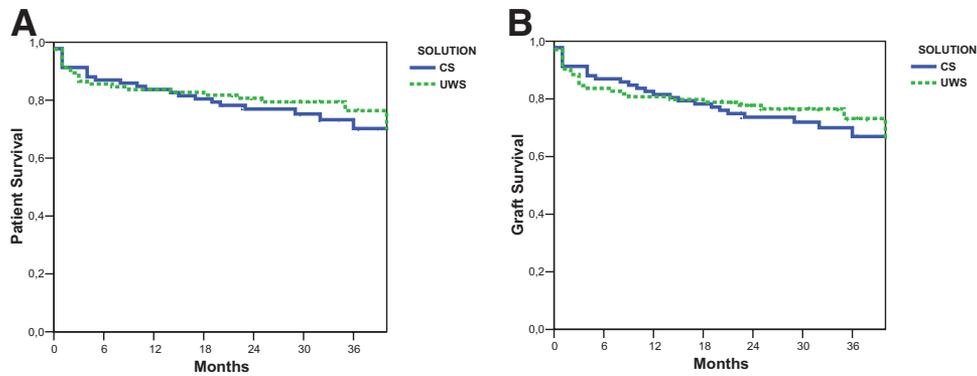
**Figure 2.** (A) Patient survival and (B) graft survival for recipients of donor livers preserved with CS or UWS in the first 3 years post-transplantation. Abbreviations: CS, Celsior solution; UWS, University of Wisconsin solution.

ginal donor or graft is broad, but it may generally be considered to refer to donors or grafts implying a higher risk of immediate, medium-term, or long-term PDF or PNF. Because livers from suboptimal or extended-criteria donors are more susceptible to damage from ischemia-reperfusion and preservation injury, PDF and PNF rates are higher with these donors.[3,4]

Modifications have been proposed to the preservation solutions currently in use with the aim of improving the preservation of organs obtained from extended-criteria donors, and new solutions are currently in the experimental and developmental stages. New liver preservation solutions should enable increased use of extended-criteria grafts and should, if it is possible, allow longer ischemia times, thereby enabling transplant waiting lists to be reduced. In the field of organ storage and transplantation, important advances have been made in our understanding of the mechanisms underlying ischemia-induced cellular injuries and, consequently, in the physiological and pharmacological development of preservation and storage solutions for tissues and cells under cold ischemia conditions.

UWS is considered the gold-standard solution for the preservation of abdominal organs (liver, kidneys, and pancreas).[8] Experiments with new preservation solutions, such as CS, have been conducted with a view toward improving organ preservation[9]; CS has certain characteristics (eg, composition) that could render it clinically useful.

The formulation of this solution addresses the same preservation problems already recognized by Belzer[2] with respect to UWS: intracellular edema, oxygen free-radical injury, and intracellular calcium overload. UWS and CS differ in composition: UWS contains the impermeant substances lactobionate and raffinose to control intracellular edema, whereas CS contains lactobionate and mannitol. Furthermore, because CS, unlike UWS, is colloid-free, its viscosity is greatly reduced (1150 $mm^2/s$ for CS versus 3159 $mm^2/s$ for UWS), and its capacity for organ perfusion is improved. With respect to free-radical injuries, CS uses reduced glutathione, which is one of the most effective antioxidants currently in use, whereas UWS uses rapidly oxidized glutathione.

The high potassium content of UWS may increase calcium-dependent vascular contractions, resulting in (among other adverse effects) a greater resistance to perfusion as a result of contracted renal glomerular capillaries, endothelial dysfunction, and subcellular lesions of the biliary tract during a prolonged cold ischemia time and also contributing to cardiac arrhythmias after clamp release if the preservation solution is not completely flushed from the organ before implantation. These problems are not, in theory, encountered with low-potassium CS.

To justify our study and its design, we point out that few prospective studies comparing these 2 preservation solutions have been reported in the literature, and most of the studies that have been published—smaller than ours—had a limited number of patients.[15-20] Our study was designed to compare CS and UWS on the basis of the hypothesis that both solutions are effective in cadaveric donor liver preservation.

It is important to stress that, in our study, the same small group of professionals was responsible for surgery in both donors and recipients, donor-recipient selection, and preoperative, perioperative, and postoperative management. The fact that they used the same procedural criteria and followed the same medical and surgical protocols ensured greater study robustness and homogeneity and reduced the risk of potential bias in the outcome analysis.

Moreover, because 1 of our study groups had the sample size reduced to 92 cases, the statistical power was consequently reduced to 77%. This was a small difference (a decrease from 80% to 77%) with very few implications, and the final difference between the 2 groups was not that significant from a clinical point of view.

The donor groups included in this study were representative in terms of the general demographic characteristics currently applied for liver graft donors.[22] Certain donor characteristics potentially affect graft function or cause graft preservation injuries.[5-7,23] We found no significant differences in our 2 series with respect to the presence or absence of these risk factors, which could have influenced and introduced bias into the study results. In particular, there were no differences in donor distribution according to gender, age,

steatosis, cause of death, hypotension episodes, or use of vasopressor drugs during clinical management.

Because determining factors in recipients can also influence results, these were also analyzed and compared in both groups. No significant differences were observed between the 2 recipient groups in terms of the distribution of viral or tumor etiology, age, or pretransplant Child-Pugh class of the recipients.

No significant differences were observed between the 2 groups for the surgical technique variables in terms of the number of cases in which the recipient vena cava was preserved, the type of recipient implant, the infusion of packed red blood cells, plasma, and platelet pools, and intraoperative blood collected by the Cell Saver.

Like other authors,[19] we observed that a smaller perfusion volume was used in the UWS group. In our series, the median difference was 250 mL, which was a small but significant difference. This difference may be explained by the lower viscosity of CS (which allows the solution to flow faster), or by the manufacturer's recommendation to use larger perfusion volumes than those recommended for UWS.

As for the primary endpoints (PNF and PDF, as defined by Ploeg et al.[4]), the rates were the same in both groups; these results, which are consistent with preclinical and clinical studies carried out in humans,[11,16-20] prove the effectiveness and equivalence of CS in comparison with UWS. Cold ischemia time ranges (a factor with a bearing on posttransplantation liver function) were not significantly different in the 2 groups. In our series, in fact, cold ischemia times were low in both groups (mean < 6 hours). Liver impairment recovery and resolution as well as mortality were likewise similar in the 2 groups.

We analyzed liver function biochemical parameters for synthesis and excretion in the 2 groups. No significant differences were found in AST levels in the follow-up sampling period during the first posttransplantation year. These results appear to indicate that CS and UWS are equivalent in terms of ischemic preservation injuries; according to Cofer et al.,[8] AST serum levels are the best indicator of ischemic preservation injury in the early postoperative period. Higher ALT levels in the UWS group were observed in our study, but only in the third postoperative month, and no initial, progressive, or steady increase was detected. We would hesitate to attribute this result to the perfusion solution, as there are many factors that might influence a patient's status in the third month after transplantation.

In our study, total bilirubin levels in the first postoperative month were higher in the UWS group compared with the CS group. Although the difference was not statistically significant, this finding could be secondary to a higher number of biliary complications. Pedotti et al.[19] also reported higher total bilirubin levels in the UWS group compared to the CS group on the fifth postoperative day; this finding was attributed to CS's protection against calcium overload, which induces calcium-dependent microvascular contractions and results

in greater resistance to perfusion and subsequent endothelial injury. The perfusion fluid viscosity has also been noted to be a factor that could influence penetration in the most distal areas of the organ's vascular tree, causing inadequate perfusion of the arterioles of the biliary tree and insufficient preservation of the bile ducts and the epithelium on which the biliary tree depends. Greater fluidity would allow better distal perfusion, which, in turn, would mean better storage and preservation of the biliary tree and fewer late biliary complications.[24,25] The study revealed no differences in the total number of biliary complications, nor did we encounter a significant proportion of ischemic-type biliary lesions, which are usually associated with preservation problems. Other studies have reported a tendency toward lower biliary complication rates in cadaveric and living grafts perfused with solutions with a lower viscosity than UWS.[24,26-28]

We found no noticeable differences between the study groups in terms of clotting factor synthesis parameters or the number of postoperative bleeding or arterial complications.

Graft and patient follow-up was extensive. The prevalence of hepatitis C virus–positive recipients was quite high,[29,30] and because it has been demonstrated that those patients have poorer graft and patient survival rates,[31,32] this variable could have had a negative influence on the CS series, which had a higher incidence of hepatitis C virus. We found no significant differences for the 2 preservation fluids in terms of patient and graft survival in the 3-year follow-up period; however, the results are consistent with those obtained in other studies, including both single-center studies such as ours[16,19,20] and multicenter studies.[18]

In conclusion, like the authors of other studies and trials, we have found that CS effectively preserves and stores liver grafts for transplantation and offers immediate functionality similar to that of UWS. During the 3-year follow-up period, we found no important differences in graft or patient survival or in the number of biliary or vascular complications. Both solutions are, therefore, appropriate for clinical use in orthotopic hepatic transplantation using cadaveric donors.

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