Combined Flush With Histidine-Tryptophan-Ketoglutarate and University of Wisconsin Solutions in Liver Transplantation: Preliminary Results

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ABSTRACT

Introduction. Ischemia reperfusion injury (IRI) is the main cause of early allograft dysfunction (EAD) and subsequent primary allograft failure (PAF).

Objectives. The purpose of this study is to compare IRI, EAD, and PAF in liver transplantation in a cohort of patients perfused with histidine-tryptophan-ketoglutarate (HTK) solution and University of Wisconsin (UW) solution versus HTK alone.

Methods. A randomized trial was performed to compare outcomes in liver recipients who underwent transplantation surgery in the University Regional Hospital of Malaga, Spain. Forty patients were randomized to two groups. Primary endpoints included IRI, EAD, PAF, re-intervention, acute cellular rejection, retransplantation, arterial complications, and biliary complications at postoperative day 90.

Results. Postoperative glutamic oxaloacetic transaminase (1869.15 ± 1559.75 UI/L vs. 953.15 ± 777.27 UI/L; $P = .004$) and glutamic pyruvic transaminase (1333.60 ± 1115.49 U/L vs. 721.70 ± 725.02 U/L; $P = .023$) were significantly higher in patients perfused with HTK alone. A clear tendency was observed in recipients perfused with HTK alone to present moderate to severe IRI (7 patients in the HTK + UW solution group vs. 15 patients in the HTK-alone solution group; $P = .06$), EAD (0 patients in the HTK + UW solution group vs. 0 patients in the HTK-alone solution group; $P = .76$), and PAF (3 patients in the HTK + UW solution group vs. 8 patients in the HTK-alone solution group; $P = .15$).

Conclusions. Initial perfusion with HTK solution followed by UW solution in liver transplantation improves early liver function as compared to perfusion with HTK alone.

ISCHEMIA reperfusion injury (IRI) is caused by a temporary impairment of the blood flow to a particular organ (ischemia) and the subsequent return of full blood (reperfusion). This process induces a series of molecular responses (leukocyte response and release of inflammatory and oxidative stress mediators) that may cause cellular damage to the organ affected and at systemic level.

Considerable efforts are being made in the field of transplantation to find a therapeutic approach that prevents IRI. This type of damage is associated with graft dysfunction and reduced graft survival [1,2]. The extent of IRI is determined by anatomopathological analysis following liver reperfusion [3,4]. IRI is associated with early retransplantation. A variety of organ preservation techniques are used to minimize IRI.

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The University of Wisconsin (UW) solution has been the gold standard in liver transplantation since the 1990s. Limitations of UW solution include its high viscosity, high potassium concentration, and elevated erythrocyte aggregation. In recent years, alternative solutions such as histidine-tryptophan-ketoglutarate (HTK) solution have gained popularity, as they are less viscous and cost-saving [5,6]. Recent studies suggest that survival is lower in liver grafts perfused with HTK solution [7]. Experimental assays in animals have revealed that the advantages of a low viscosity solution (HTK) combined with those of a high viscosity solution (UW) could reduce IRI [8,9].

METHODS

Study Design

This randomized clinical trial was approved by the Ethics Committee of the Regional University Hospital of Malaga, Spain. The study involved patients who underwent liver transplantation locally after providing informed consent.

In a previous study [8] in animal models who received either HTK + UW solution or HTK solution alone, the maximum alanine aminotransferase reported for the HTK + UW solution group was 422 ± 186 mU/L/g versus 735 ± 237 mU/L/g for the HTK solution group. Sample size was calculated assuming the maximum GOT value reported. However, to reach significance in severe IRI, a huge sample of individuals would be necessary. If 40 individuals were enrolled in each group, the study would have a 99% power to detect significant differences by bilateral Student *t* test with independent samples at a 5% level of significance, assuming that the means for the HTK-alone solution and the HTK + UW solution groups were 735 and 422, respectively, and standard deviation for the two groups was 263.

Patients were randomized to receive either a combined perfusion or a perfusion alone (n = 40 each). In this report, we present the outcomes for the first 20 patients assigned to each group who underwent transplantation locally between July 2015 and January 2017. Inclusion criteria were that brain-dead donors were used for liver transplantation as well as locally procured and transplanted organs. Exclusion criteria were liver extractions that were not performed locally, use of living donors or donors in asystole, biliary-digestive anastomosis, or an indication of fulminant hepatitis.

Randomization was performed using the Epidata statistical package (Epidat 3.1. Health Council of Galician Regional Government, Spain) by which patients were randomly assigned to one of the groups. Randomization was blinded to the liver transplantation surgery team, physicians involved in in-hospital follow-up examinations, anatomopathologists, and hepatologists in charge of outpatient follow-up.

Donor Organ Preservation

The first group was perfused with 4 L of HTK solution via an aortic arterial cannula plus 2 L of HTK solution via a portal venous cannula. Once the liver was extracted, it was washed out with 1 L of UW solution before being introduced into a bag. During bench surgery, the organ was flushed with 1 L of UW solution. In contrast, in the other group, patients and grafts were perfused with the same volumes of HTK solution as the first group, but UW solution was not used.

Score of Severity of IRI

Surgical biopsy specimens were obtained intraoperatively after complete revascularization of the graft, typically after biliary anastomosis (less than 1 hour) [4]. The score of severity of IRI was determined according to the presence of neutrophilic infiltrate, apoptosis, and hepatocyte cell dropout. Based on these factors, 4 degrees of severity were established: nil, mild, moderate, and severe.

Statistical Analysis

Differences between mean values were evaluated using the Student *t* test or the Mann-Whitney U test. Differences between the two groups in categorical variables were evaluated using the χ^2 test. Odds ratios and their corresponding confidence intervals were calculated at 95% for bidimensional tables. Data were processed using SPSS 17.0 software (SPSS Inc., Chicago, Illinois, United States). A P value $\leq .05$ was considered statistically significant.

RESULTS

Donor, receptor, and postoperative variables are shown in Table 1. No statistically significant differences were observed between the two groups, except for intensive care unit stay (3.20 ± 4.26 days for the HTK-alone solution group vs. 2.25 ± 1.71 days for the HTK + UW solution group; $P = .03$). Postoperative glutamic oxaloacetic transaminase (GOT) (1869.15 ± 1559.75 UI/L vs. 953.15 ± 777.27 UI/L; $P = .004$) and glutamic pyruvic transaminase (1333.60 ± 1115.49 U/L vs. 721.70 ± 725.02 U/L; $P = .023$) were significantly higher in patients perfused with HTK solution alone. A clear tendency was observed in recipients perfused with HTK solution alone to present moderate to severe IRI (7 patients in the HTK + UW solution group vs. 15 patients in the HTK-alone solution group; $P = .06$), early allograft dysfunction (EAD) (0 patients in the HTK + UW solution group vs. 0 patients in the HTK-alone solution group; $P = .76$), and primary allograft failure (3 patients in the HTK + UW solution group vs. 8 patients in the HTK-alone solution group; $P = .15$).

DISCUSSION

The purpose of this study was to assess the potential benefits of perfusing liver grafts initially with a low-viscosity solution and subsequently using a more viscous solution for perfusion and preservation. In the 1990s, the UW solution was considered the gold standard for long-term organ preservation. According to several studies [10], the high viscosity − caused by red blood cell hyper aggregation − of the UW solution may result in a poor distribution in the graft. In contrast, the HTK-alone solution shortens the period of cold storage and is less viscous, being more effective for the wash-out and rapid cooling of the graft [11]. Recent studies suggest that the survival rate is lower in liver grafts perfused with HTK solution alone [7].

On the other hand, initial perfusion with HTK solution may facilitate wash-out and rapid cooling of the liver graft and allow long-term preservation in a UW solution. The results obtained in the study show lower liver enzyme peaks within 7 postoperative days, and lower rates of early allograft dysfunction [12], in favor of combined perfusion.