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Compared efficacy of University of Wisconsin and histidine-tryptophan-ketoglutarate solutions in *ex-situ* liver resection and autotransplantation for end-stage hepatic alveolar echinococcosis patients

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ABSTRACT

Background: The University of Wisconsin (UW) and histidine-tryptophan-ketoglutarate (HTK) solutions are the two most frequently used liver graft preservation fluids. The present study aimed to compare their efficacy in end-stage hepatic alveolar echinococcosis patients who underwent *ex-situ* liver resection and autotransplantation (ELRA).

Methods: A total of 81 patients received ELRA from August 2010 to March 2018. They were allocated into UW ($n=48$) and HTK groups ($n=33$) based on the type of solutions used. Demographic and operational data were retrospectively analyzed. Primary outcomes included 90-day mortality, incidence of early graft loss, primary dysfunction, and postoperative complications.

Results: Demographic and operational characteristics were similarly distributed in the two groups. No statistically significant differences were observed with regard to 90-day mortality (12.77% vs. 12.12%) and early graft loss rate (8.51% vs. 9.09%) between the two groups. Patients in the UW and HTK groups showed a primary dysfunction rate of 27.66% and 27.27%, respectively. The UW group exhibited a higher incidence tendency of biliary complications, albeit with no statistical significance.

Conclusions: This is the largest cohort study comparing the efficacy of the UW and HTK organ-preserving solutions in end-stage hepatic alveolar echinococcosis patients in ELRA settings. UW and HTK solutions presented similar efficacy and safety. A randomized clinical trial with larger scale is needed for further investigation in future clinical applications.

Introduction

Liver transplantation (LT) has been the major radical modality for patients with end-stage liver diseases and has profoundly improved the prognosis. Advances and innovative discoveries regarding novel immunosuppressant agents and organ preservation solutions have tremendously improved both short- and long-term outcomes [1]. *Ex-situ* liver resection and autotransplantation (ELRA) has emerged as an alternative surgical option in some end-stage liver diseases that once were conventionally unresectable or listed only for LT. Similar to the conventional transplantation procedure, ELRA requires perfusion with an organ-preserving solution during the anhepatic phase prior to the implantation process. University of Wisconsin (UW), histidine-tryptophan-ketoglutarate (HTK) and Celsius solutions, among others, have been reported for application to ELRA [2,3].

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UW, which was first introduced in the late 1980s, has been widely used and has shown superior clinical outcomes [4] and was even once considered the gold standard preservation solution for LT, while HTK was initially applied in cardiac surgery and recently began to be adopted for routine use for liver, kidney and pancreas preservation [5,6]. The selection of preservation solutions is regarded as one of the essential factors affecting transplantation outcome. The efficacy of UW and HTK solutions was compared in a large-scale clinical cohort studies and randomized clinical trials in living donor LT [7,8] and deceased donor LT settings [5,9–16]. Both solutions manifested their own inherent advantages and disadvantages that were closely related to their compositions [9]. However, only inconclusive and controversial results were yielded, ranging from equality to favoring one or the other solution [12]. The inconsistency of research outcome might be attributed to the size of the sample and the quality of the study.

During the 10-year period, our institution successfully carried out ELRA on 81 end-stage hepatic alveolar echinococcosis (AE) patients as the largest cohort in the world, to the best of our knowledge. To date, the impact of mainstream organ preserving solutions in ELRA is missing. Herein, we aimed to compare the efficacy and safety of UW and HTK solutions focusing on 90-day patient survival, liver graft primary dysfunction (PDF), postoperative complications, and intraoperative metabolic as well as hemodynamic stability in large cohort ELRA settings.

Methods

Patients

This study is in compliance with the *Declaration of Helsinki* (2013) [17] and was approved by the ethics committee of our institution. Informed consent was obtained from all the subjects and/or their legal guardians.

From August 2010 to March 2018, 81 end-stage hepatic AE patients underwent ELRA. The resectability and operability of the patients were carefully assessed by a multidisciplinary team including hepatobiliary surgeons, hepatologists, interventional therapists, radiologists, and anesthesiologists. The indication of the ELRA and standard treatment flow was clearly shown in the previous studies [18,19]. Of note, during the study period, three patients with end-stage haptic AE were subjected to LT due to cirrhosis, Budd-Chari syndrome and insufficient residual liver volume and were excluded from the present study. One patient with leiomyosarcoma from inferior vena cava origin was treated by ELRA and was not included in the current study.

Preoperative assessment

Laboratorial results, including routine blood tests, liver function tests, coagulation tests, and *Echinococcus multilocularis* (*E. multilocularis*) specific antigen serology tests, were examined in all subjects. Computed tomography (CT), magnetic resonance imaging and whole-body positron emission tomography (PET)-CT scanning were applied to assess the lesion site, size, vascular and biliary involvement as well as remote organ metastasis. A three-dimensional volumetric assessment was carried out to calculate the estimated graft volume.

Surgery

ELRA was performed as previously described. Briefly, after successful access to the abdominal cavity, we isolated perihepatic ligaments and vasculatures, and explanted the whole liver into an ice basin. Subsequently, two independent teams performed bench resection and hemodynamic control, respectively. No veno-venous bypass was introduced; instead, temporary inferior vena cava reconstruction and portosystemic shunts were performed as previously described [18,19].

Data collection

Demographic information including age, sex, occupation, body mass index (BMI), previous anti-parasitic therapy and abdominal surgery, and model for end-stage liver disease (MELD) scores [20] were collected. Intraoperative parameters, including channel and volumes of organ preserving solution, surgical time, and anhepatic phase duration, were retrieved. The warm ischemia time in this study was relatively short (approximately 1–3 min) that could be negligible. In addition, metabolic and hemodynamic parameters containing serum potassium and sodium levels and mean arterial/central venous pressure were recorded at the beginning of anesthesia, just before and after reperfusion, respectively. Hypotension after reperfusion is defined by a decrease in mean arterial pressure (MAP) to more than 30% below the baseline value [21].

Primary outcomes

The primary outcomes included 90-day mortality, incidence of PDF of liver graft, early graft survival (proportion of autograft survival in the first three months), and postoperative complications. Initial primary failure (IPF) is defined as the presentation of one or more of the following variables: (i) bilirubin $\geq$10 mg/dL (171 μmol/L) on postoperative day 7 (POD 7); (ii) INR $\geq$1.6 on POD 7; (iii) ALT or AST >2000 IU/L within POD 1–7. Death or need for retransplantation after operation is considered primary nonfunction (PNF) [22]. The number of PDFs was calculated as the total sum of the number of IPFs and PNFs. The peri–operative laboratory results and intraoperative metabolic and hemodynamic stability parameters were also analyzed.

Follow-up

Laboratorial parameters, including routine blood tests, liver function tests, and coagulation analyses during the peri–operative period, were examined at POD 0–7, 14 and 30. All surviving patients were carefully followed-up with liver function tests, serology tests, ultrasonography, and CT and PET-CT scans, which were carried out to assess the size and quality of the graft liver, as well as possible recurrence. The routine tests were performed at 0.5, 1, 2, 3, 6, 12, and 24 mon after discharge. CT scan was performed 3–6 mon and 12 mon post-discharge. PET-CT may be considered based on the results indicating for recurrence or metastatic lesion.

Statistical analysis

All data were analyzed using Statistical Package for Social Science (SPSS), version 22.0 (SPSS, Inc., Chicago, IL, USA). For continuous data in a normal distribution, values are presented as mean ± standard deviation (SD) unless otherwise stated and were compared using independent Student's *t*-test or repeated-measures ANOVA analysis as appropriate. For skewed data, values with median (interquartile) or median (range) are applied using nonparametric test for comparison. Pearson's Chi-square test was used for comparing PDF, IPF, PNF and other incidence rate analyses. Survival analysis was applied using Kaplan-Meier analysis followed by the log-rank test. Statistical significance was set at $P \leq 0.05$.

Table 1
Patient demographic information categorized by preservation solution.

Characteristics	Total ($n=81$)	UW group ($n=48$)	HTK group ($n=33$)	P value
Age (yr)	36.23 ± 11.75	36.69 ± 12.70	35.58 ± 10.37	0.678
Sex				0.064
Male	37 (45.68%)	26 (54.17%)	11 (33.33%)	
Female	44 (54.32%)	22 (45.83%)	22 (66.67%)	
BMI (kg/m^2)	21.70 ± 3.10	21.41 ± 3.15	22.12 ± 3.01	0.317
Occupation				0.132
Peasant	57 (70.37%)	36 (75.00%)	21 (63.64%)	
Civil worker/Staff	10 (12.35%)	3 (6.25%)	7 (21.21%)	
Others	14 (17.28%)	9 (18.75%)	5 (15.15%)	
MELD	3.79 ± 4.89	4.20 ± 5.25	3.10 ± 4.21	0.340
Previous abdominal surgery	34 (41.98%)	16 (33.33%)	18 (54.54%)	0.509
Partial hepatectomy	11 (13.58%)	6 (12.50%)	5 (15.15%)	
PTCD	6 (7.41%)	3 (6.25%)	3 (9.09%)	
Portal vein embolization	3 (3.70%)	0	3 (9.09%)	
Other	14 (17.28%)	7 (14.58%)	7 (21.21%)	
Previous chemotherapy	26 (32.10%)	15 (31.25%)	11 (33.33%)	0.844

BMI: body mass index; MELD: model for end-stage liver disease; PTCD: percutaneous transhepatic catheter drainage.

Results

Demographic results

All patients experienced successful ELRA with zero intraoperative mortality. Of the reported 81 patients, the procured liver in 48 (59.26%) patients was flushed/preserved with UW solution, while the liver in the remaining 33 (40.74%) patients was flushed/preserved in HTK solution. The use frequencies of the UW solution decreased from the first period of study (2010–2014) 100% to 46.77% during the latter stage (2015–2018) when the usage of HTK sharply increased from 0% to 53.23%. Basic demographic information between the two groups was similar, as shown in Table 1. The mean age was 36.69 ± 12.70 years in the UW group and 35.58 ± 10.37 years in the HTK group ($P=0.678$). The two groups were similar in sex, BMI and occupational distribution. *E. multilocularis*-specific antigen test results were displayed as the proportion of antigen-positive intensity for four *E. multilocularis*-specific antibodies (Fig. 1), which showed similar distribution in two groups. Patients in the UW group presented a slightly higher mean MELD score than the HTK group, albeit with no statistical significance (4.20 ± 5.25 vs. 3.10 ± 4.21, $P=0.340$). Sixteen patients (33.33%) in the UW group and 18 (54.55%) in the HTK group had a previous abdominal surgery history. The informed surgery types and other detailed baseline information are in Table 1.

Operational characteristics

A total of 77 patients (46 in the UW group and 31 in the HTK group) presented extensive hepatic AE lesions involved in more than 3 Couinaud hepatic segments, and some patients (UW 14 and HTK 7) were found to have remote organ metastasis that were properly managed during the operation. The autograft mass and autograft-to-body weight ratio were similar in the two groups. The mean perfusion volume of UW 2438 ± 480 mL and HTK 2576 ± 502 mL via the portal vein were used, and flushing through the proper hepatic artery (55.63 ± 8.23 mL vs. 58.79 ± 6.96 mL, $P=0.215$) and common bile duct (116.67 ± 74.62 mL vs. 150.61 ± 67.41 mL, $P=0.075$) was carried out, and no significant difference was observed.

Table 2
Clinical and intra-operative characteristics of patients in groups.

Clinical details	Total ($n=81$)	UW group ($n=48$)	HTK group ($n=33$)	P value
Location of hepatic AE lesion (>3 segments)	77 (95.06%)	46 (95.83%)	31 (93.94%)	1.000
Remote organ metastasis	21 (25.93%)	14 (29.17%)	7 (21.21%)	0.422
Child-Pugh score				0.347
A	73 (90.12%)	45 (93.75%)	28 (84.85%)	
B	8 (9.88%)	3 (6.25%)	5 (15.15%)	
Comorbidity	16 (19.75%)	11 (22.92%)	5 (15.15%)	0.388
Perfusing/flushing volume (mL)	2681.23 ± 546.95	2609.78 ± 533.82	2785.15 ± 557.28	0.158
Portal vein	2493 ± 490	2438 ± 480	2576 ± 502	0.215
Proper hepatic artery	56.91 ± 7.85	55.63 ± 8.23	58.79 ± 6.96	0.215
Common bile duct	130.49 ± 73.28	116.67 ± 74.62	150.61 ± 67.41	0.075
Autograft mass (g)	844.63 ± 267.10	801.67 ± 257.88	907.12 ± 271.82	0.081
Autograft-to-body weight ratio	14.70 ± 5.21	14.03 ± 5.35	15.68 ± 4.92	0.164
Simultaneous operation	23 (28.40%)	14 (29.17%)	9 (27.27%)	0.853
Surgical time (min)	993.61 ± 183.52	973.32 ± 138.41	1046.58 ± 204.78	0.058
Hospital stay (d)	40.78 ± 22.25	38.81 ± 22.16	43.64 ± 22.42	0.341
ICU stay (d)	6.32 ± 8.82	5.38 ± 7.03	7.7 ± 10.89	0.247
Anhepatic phase (min)	381.89 ± 132.89	343.81 ± 127.88	387.27 ± 101.62	0.107
Blood loss (mL)	1954.94 ± 2439.90	1707.29 ± 2043.67	2315.15 ± 2919.35	0.273
Blood supplements				
Red blood cells (UI)	7.58 ± 7.01	7.31 ± 6.25	7.96 ± 8.07	0.684
Fresh frozen plasma (mL, median, interquartile)	745 (547.5–1200)	630 (520–1060)	840 (550–1700)	0.054
Autotransfusion (mL)	527.57 ± 676.86	488.40 ± 701.96	584.55 ± 644.96	0.533
T-tube	10 (12.35%)	5 (10.42%)	5 (15.15%)	0.770

AE: alveolar echinococcosis; ICU: intensive care unit.

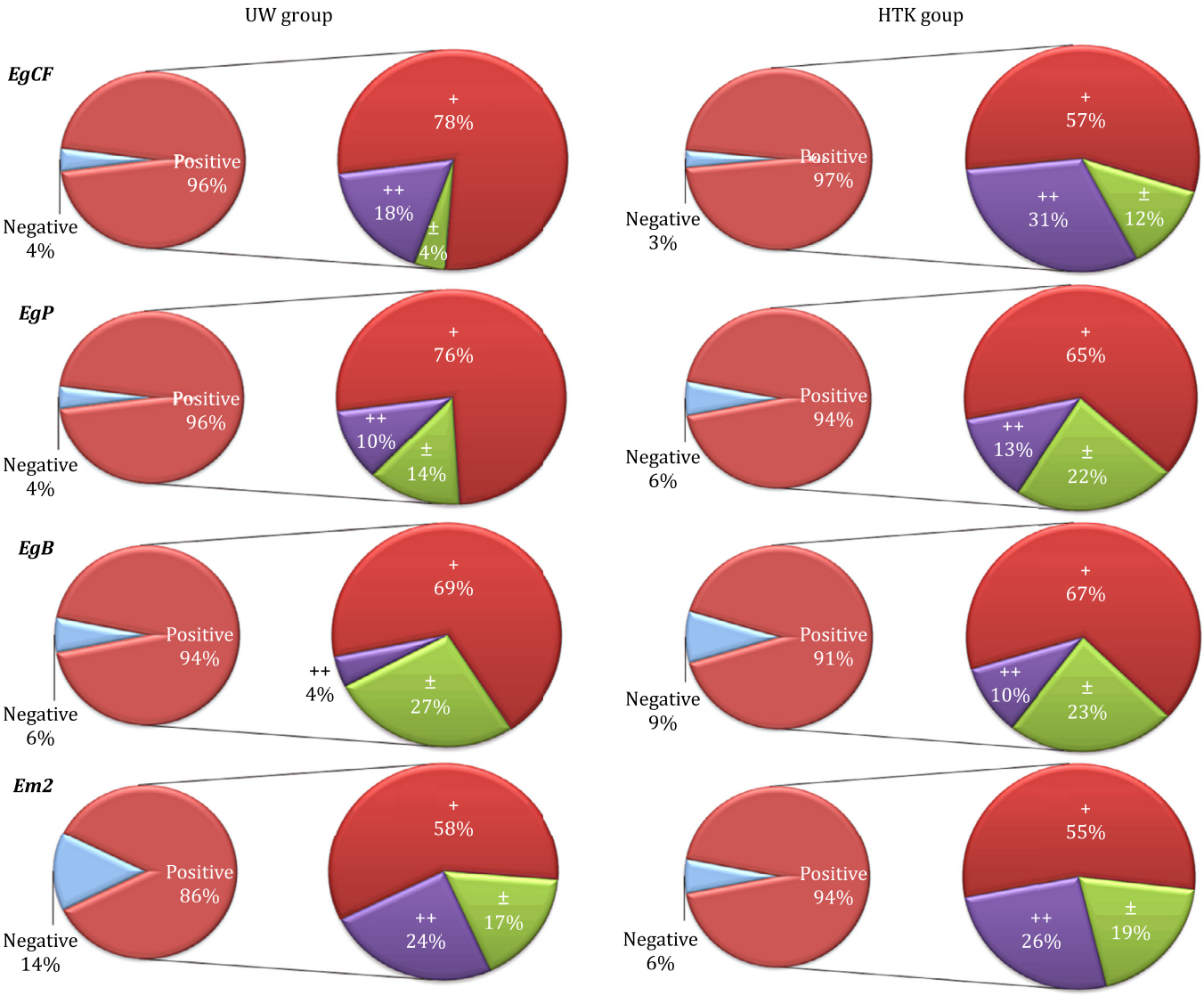

Fig. 1. *E. Multilocularis*-specific antigen test results in two groups. Specific antigens of *EgCF*, *EgP*, *EgB* and *Em2* were displayed as the proportion of positive intensity. The overall proportion of positive results for each antigen was similar in two groups.

Surgical time, anhepatic phase duration, postoperative hospital and intensive care unit (ICU) stays were of the similar length. Differences in blood loss and use of blood products such as red blood cells, fresh frozen plasma and autotransfusion volumes between the two groups were not statistically significant. T-tubes were placed in five patients in each group (Table 2) and drawn according to postoperative recovery conditions.

Primary outcomes

The median follow-up time was 17.42 (range 0.27–86.10) months in the UW group and 12.87 (range 0.10–37.00) months in the HTK group. One patient was lost to follow-up, 10 patients (UW 6 and HTK 4) died. Postoperative 90-day mortality was slightly higher in the UW group than in the HTK group (12.77% vs. 12.12%, $P=1.000$). Survival outcomes were not significantly different between groups, as the 1-, 2- and 6-month overall survival rates (UW group vs. HTK group) were 91.49% vs. 87.88%, 89.36% vs. 87.88% and 87.23% vs. 87.88%, respectively ($P=0.969$, Fig. 2). The reasons for death in the UW group were multiple organ dysfunction syndrome ($n=4$), intra-abdominal bleeding ($n=1$), and sepsis ($n=1$). In the HTK group, the deaths were attributed to hepatic failure ($n=2$), intra-abdominal bleeding ($n=1$) and multiple organ dysfunction syndrome ($n=1$). The PDF rates in the UW and HTK groups were 13 (27.66%) and 9 (27.27%), respectively. Accordingly, IPF rates in the UW and HTK groups were 7 (14.89%) and 5 (15.15%), respectively. A total of 10 patients (12.50%, UW/HTK: 6/4) had PNF. All IPF patients' conditions were improved after careful monitoring and management. Early graft loss occurred in 4 patients in the UW group and 3 in the HTK group (8.51% vs. 9.09%, Table 3).

The major complications were pleural effusion, ascites and biliary leakage. A tendency toward a high incidence of biliary leakage in the UW group (14.89%) were found compared to that in the HTK group (3.03%); however, there were no significant differences ($P=0.668$) Two hepatic thromboses occurred in the UW group and one in the HTK group, and the latter case developed into two biliary stenoses that were treated with proper management.

Peri-operative laboratory results and intraoperative metabolic and hemodynamic stability parameters

Two groups exhibited persistently higher mean levels of serum ALT and AST. Although a gradually decreasing trend was observed after POD 1, the magnitude was lower in the HTK group. At

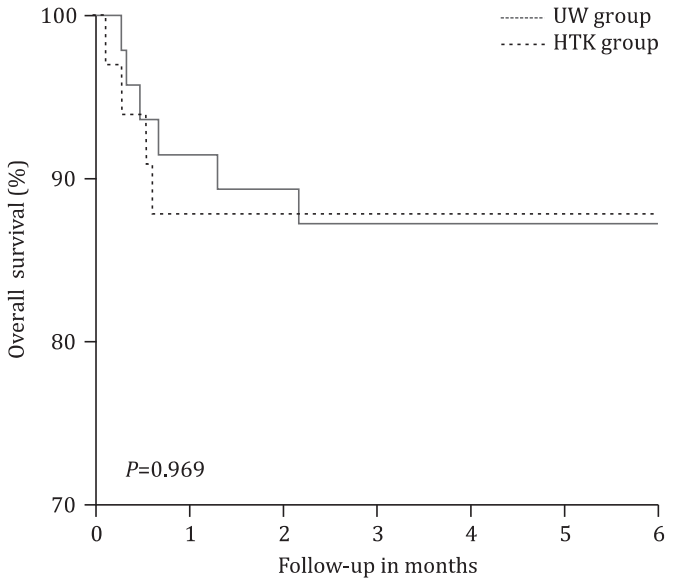

Fig. 2. The 1-, 2- and 6-month patient overall survival for UW and HTK solutions. (Kaplan-Meier analysis, $P = 0.969$).

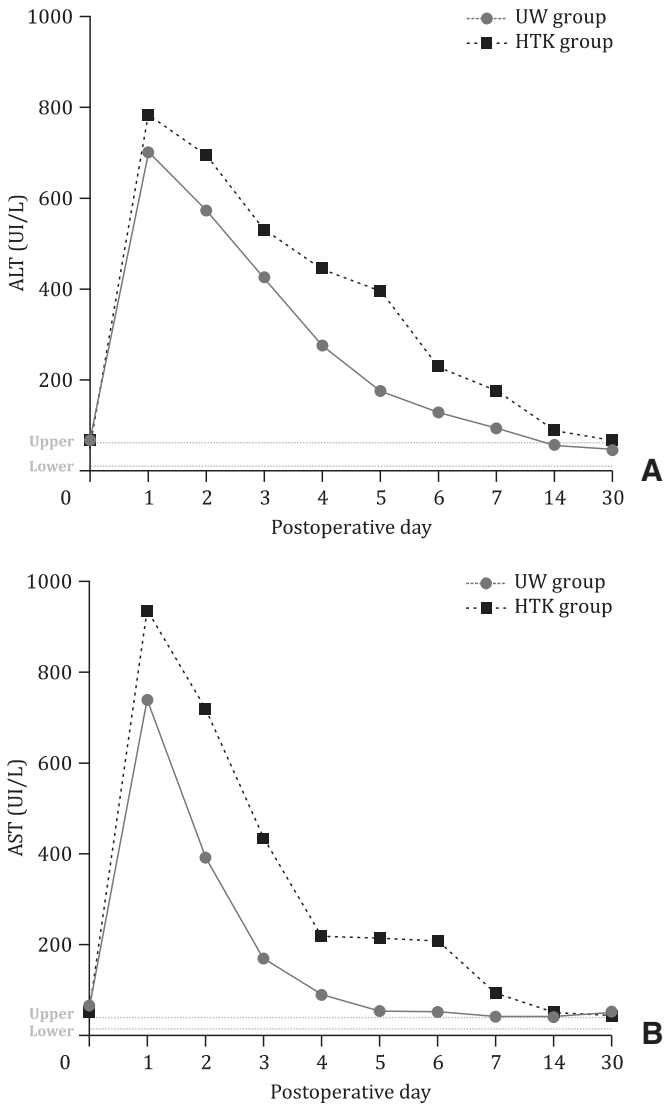

Fig. 3. Mean serum levels of ALT (**A**) and AST (**B**) in UW and HTK groups. HTK groups presented slight higher levels of ALT and AST compared with HTK group with no statistical differences (independent Student's *t*-test, $P>0.05$). The dashed lines represented for the upper and lower limit based on the normal range at our center.

POD 14, the ALT and AST levels were similar between the two groups. Notably, no significant differences were found between them throughout the designated time-points (Fig. 3).

Levels of white blood cell counts that present inflammatory responses were higher than the upper normal levels during postoperative periods and reached normal values at POD 30. Both the eosinophil cell count (EO#) and percentages (EO%) as well as creatinine were all within the normal range and similar in the two groups. Peri-operative serum hemoglobin and albumin levels during all observed time-points were below the lower limit without significance between two groups. Total and direct bilirubin presented a rapid increase after the operation, reached its peak on POD 5 and gradually decreased. Platelet counts displayed a sharp decrease at POD 1, remained under the lower limit until POD 5 and then remained within the normal range. The HTK group presented significantly lower prothrombin time ratios at POD 4, 5 and 14 compared to those in the UW group (Fig. 4).

Although basic serum sodium levels in the HTK group differed significantly from those in the UW group, their levels throughout the surgical procedure were within normal limits and did not change significantly after reperfusion. Both the UW and HTK groups displayed a significant reduction in mean serum potassium levels but were still within the normal range. Body temperature changes were similar between groups. The HTK group presented a significantly decreased MAP from prereperfusion to postreperfusion, but the changes in MAP were not significantly different in the UW group. All MAP values were within the normal range, and there was no case of hypotension (Table 4).

Discussion

Herein, we present the largest cohort study of ELRA, to the best of our knowledge, comparing the efficacy of the organ preserving solutions UW and HTK. Our results claimed similar clinical outcomes regarding postoperative mortality, PNF, early graft loss, biliary complications and intraoperative metabolic and hemodynamic alterations in patients undergoing ELRA involving preservation with both UW and HTK.

ELRA was first reported by Schlitt et al. [23] in a patient with gastric leiomyosarcoma liver metastasis. Since then, this challenging technique has been sporadically practiced in conventionally unresectable patients. To date, more than 200 patients have been reported to undergo ELRA. During this period, our institution has successfully performed this procedure to treat 81 end-stage hepatic AE patients and has obtained promising clinical outcomes. In contrast to conventional LT, ELRA requires neither organ donors nor posttransplant immune-suppressive agents and thus is becoming an alternative option in selected cases. There are several factors that may influence the outcome of ELRA; among them, the preservation solution is one of the critical factors that influence the clinical outcomes of patients. Various types of organ preserving solutions have been introduced into organ transplant surgery and to date, UW and HTK have been commonly practiced worldwide. Both solutions show their inherent advantages and disadvantages because the compositions included are different. Studies that compare the outcome of UW and HTK in LT patients are controversial and inconclusive in different clinical settings.

Erhard et al. [10] reported the first prospective randomized clinical trials that compared the clinical efficacy of UW and HTK with similar overall outcomes but with increased hepatocellular

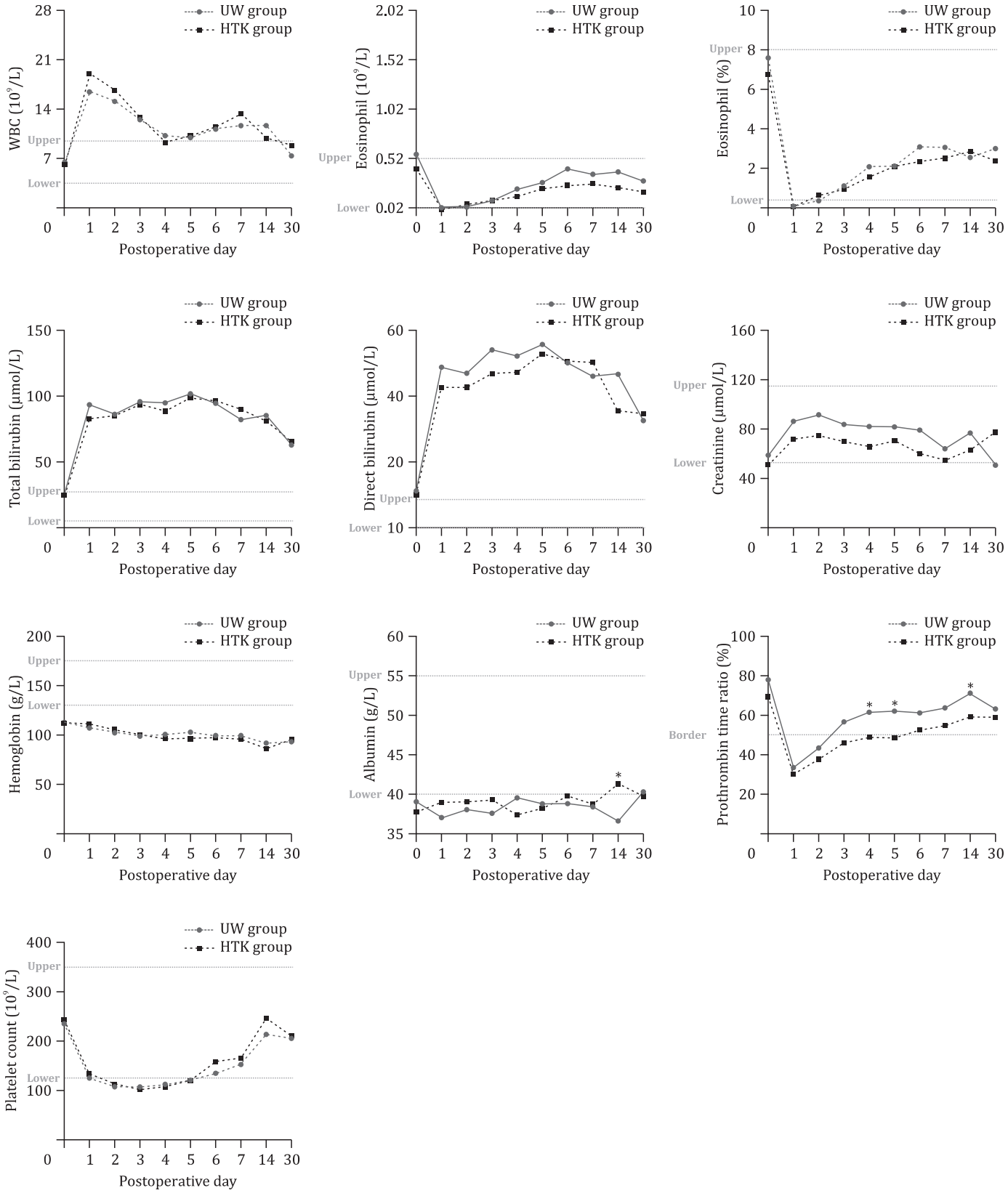

Fig. 4. Comparison of peri–operative laboratorial results between in the UW and HTK groups. $^*P < 0.05$.

Table 3
Incidence of primary dysfunction and postoperative complications in groups.

Incidences	Total* ($n=80$)	UW group* ($n=47$)	HTK group ($n=33$)	P value
Primary dysfunction	22 (27.50%)	13 (27.66%)	9 (27.27%)	0.970
Initial primary failure	12 (15.00%)	7 (14.89%)	5 (15.15%)	0.980
Primary nonfunction	10 (12.50%)	6 (12.77%)	4 (12.12%)	1.000
Early graft loss	7 (8.75%)	4 (8.51%)	3 (9.09%)	1.000
Postoperative complications				
Pleural effusion	25 (31.25%)	14 (29.79%)	11 (33.33%)	0.736
Ascites	12 (15.00%)	5 (10.64%)	7 (21.21%)	0.324
Biliary complications	10 (12.50%)	7 (14.89%)	3 (9.09%)	0.668
Leakage	8 (10.00%)	7 (14.89%)	1 (3.03%)	
Stenosis	2 (2.50%)	0	2 (6.06%)	
Pneumonia	5 (6.25%)	2 (4.26%)	3 (9.09%)	0.681
Thrombosis	3 (3.75%)	2 (4.26%)	1 (3.03%)	1.000

* one patient was lost to follow-up.

Table 4
Changes of metabolic and hemodynamic variables at three time-points in groups.

Parameters	UW group ($n=41$)*	HTK group ($n=29$)*	P value[a]
Na^+ (mmol/L)			
Start-operation	139.02 ± 4.21	140.97 ± 3.21	**0.041**
Before-reperfusion	150.98 ± 16.98	148.34 ± 5.38	0.975
After-reperfusion	147.88 ± 3.49	148.69 ± 5.25	0.471
P value[b]	0.429	0.424	
K^+ (mmol/L)			
Start-operation	3.55 ± 0.57	3.46 ± 0.33	0.408
Before-reperfusion	3.70 ± 0.58	3.74 ± 0.45	0.782
After-reperfusion	3.47 ± 0.55	3.47 ± 0.46	0.995
P value[b]	**0.002**	**0.008**	
Body temperature (°C)			
Start-operation	36.58 ± 1.77	36.25 ± 0.46	0.328
Before-reperfusion	36.51 ± 2.18	36.15 ± 1.20	0.418
After-reperfusion	36.45 ± 2.07	36.28 ± 0.95	0.167
P value[b]	0.564	0.649	
Mean arterial pressure (mmHg)			
Start-operation	84.88 ± 11.39	86.85 ± 14.58	0.527
Before-reperfusion	82.19 ± 17.47	84.36 ± 15.23	0.593
After-reperfusion	79.49 ± 14.49	77.43 ± 11.68	0.529
P value[b]	0.332	**0.046**	
Mean central venous pressure (mmHg)			
Start-operation	6.62 ± 3.28	7.00 ± 3.24	0.628
Before-reperfusion	7.54 ± 4.97	8.11 ± 3.97	0.611
After-reperfusion	6.75 ± 3.77	7.25 ± 4.17	0.603
P value[b]	0.222	0.204	

* Only available data.
[a] comparison between UW and HTK group at different time-points;.
[b] comparison within the UW or HTK group at before- vs. after-reperfusion.

injury in the HTK group. Nevertheless, higher late biliary complications in the UW group were observed without any statistical significance [24]. In line with the above study, similar efficacy and safety of two preservation solutions regarding the clinical outcomes were also published in different centers [5,8,13]. In contrast, some studies showed better graft survival and fewer biliary complications with the use of UW solutions [9,14,15].

Our results showed no difference regarding 90-day mortality, PDF rates and early graft survival. According to the new scoring system, survival outcomes following liver transplantation (SOFT) score, proposed by Rana et al. [25,26], which include 18 risk factors, had proven to be an accurate predictor of 3-month survival after liver transplantation. Previous abdominal surgery history of patients was listed as a significant recipient risk factor. In the present study, previous partial hepatectomy (UW/HTK, 6/5), percutaneous transhepatic catheter drainage (3/3), portal vein embolization (0/3) and other abdominal operations (7/7) were performed. Although the comparison between two groups resulted in no statistical significance, this recipient risk factor should, to some extent, induce bias in the results especially in 90-day mortality rate results. The possible impacts of preservation solutions on the onset of biliary complications are still a matter of controversy [12]. Regarding the postoperative complications, the UW group presented a slightly higher occurrence of biliary complications but lower pleural effusion, ascites and pneumonia complication rates than the HTK group. It is acknowledged that HTK was identified to have low viscosity, providing better procurement of biliary trees and speeding the cooling of organs [10]. Tullius et al. [27] reported that UW solutions at low temperature conditions easily form adenosine crystals that may occlude the capillary hepatic artery supplying bile ducts. Therefore, in this sense, the superiority of the HTK solution with respect to biliary complications might be partially explained. The slightly higher postoperative ALT and AST levels in the HTK group might be explained by the increased hepatocellular injury occurring when HTK was flushed into the liver and thus require further pathological confirmation. Unfortunately, histopathological evaluations in preserved tissues were absent in the present study but will be included in our future clinical practice.

The electrolyte combination, buffering capacity and viscosity of an organ preservation solution may differ according to their own composition [5,28]. An average volume of 2.79 L HTK solution was

applied in the present study, and this volume was 0.18 L more than that of the UW solution. This difference is possibly due to the lower viscosity of HTK and higher flushing speed. On average, the graft preservation time was markedly shorter in ELRA than in LT, and this is a critical factor contributing to the smaller amount of preservation solutions. Though a larger amount of HTK solution than of UW solution was used, the costs varied drastically between them, and cost-effective analysis resulted in a mean cost savings of RMB 5676.55 per patient when the HTK solution was used. Previous studies supported our results by indicating HTK as a cost-friendly preservation solution [5,7,14]. Based on ours and others' epidemiological and clinical data, it is well acknowledged that AE is more prevalent in poorly resourced pastoral areas around the world, and the high treatment expenditure, especially for ELRA, means a huge financial burden for patients from rural regions. Therefore, the switch from UW to HTK with the study time flow in this cohort could be due to the relatively low cost of HTK compared with that of UW, which would alleviate the financial burden for patients.

ELRA is characterized by complex bench resection during which metabolic and hemodynamic stability control is vitally important. In the analysis of the underlying impact of preservation on metabolic and hemodynamic stability, the alteration of related parameters was observed. Despite the high potassium component, UW showed significantly decreased potassium levels after reperfusion. This finding may indicate that prereperfusion with saline in the present study was enough to clear the side effect of hyperkalemia, especially for UW solutions [29] and was sufficient to prevent a lethal hyperkalemia condition [30].

Vasoactive substances may be the most critical factor in the alteration of vascular tone that leads to hemodynamic instability during the reperfusion period in liver transplantation [21,28,30]. Comparative results proposed that grafts preserved in HTK solution may release more vasodilatory substances than grafts in UW solution [31]. In addition, a major component of the HTK solution, histidine, could be transformed into the significant vasodilator histamine, allowing for greater length of provisional vasodilatation [21,30,31]. Such a condition might partially explain the significant reduction in MAP in the HTK group. In addition, the slight dropping of MAP in the UW group might be partially explained by the possible vasoconstriction effects of high potassium levels in UW solutions [32]. Notably, despite the decrease in MAP during the anhepatic phase in both groups, it was still within the normal range and thus may have trivial clinical significance.

There are some limitations in this study. Firstly, this study compared the clinical efficacy of UW and HTK solutions in an ELRA setting that is reserved only for highly selected cases in a single-center, thus explaining the relatively small number of patients during the 8-year study period. The heterochronic nature of the current study may, to some extent, compromise the obtained results when improved surgical techniques were taken into account; however, this is the only available large cohort study that compares the clinical efficacy of organ preservation solutions in ELRA. Thirdly, compared with living donor LT and donation after cardiac death settings, ELRA has a shorter length of graft preservation time, and this, in some sense, may weaken the potential influence of preservation solutions on graft function and patient outcomes. Lastly, the previous abdominal surgery in patients in both groups should be a confounding factor that has certain impacts on 90-day post-ELRA mortality.

In conclusion, our results showed the equal clinical effects of UW and HTK solutions with respect to patient and graft survival as well as postoperative biliary complications in ELRA. Both solutions seemed to be safe and had no negative impacts on metabolic changes. HTK solution appeared to be more cost-friendly than UW solution when financial issues were taken into consideration.

Contributors

WH conceived and designed this study. AS and TT drafted the manuscript. LT, AT, ZJM, SYM and WH performed the study and interpreted clinical data. PJ participated in clinical data collections. AS collected anesthesia records, analyzed and interpreted clinical data. TT critically revised the manuscript. WH supervised the study protocol and reviewed the manuscript. AS and TT contributed equally to this article. All authors approved the final version of manuscript. WH is the guarantor.

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Ethical approval

This study was approved by the Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University (No. 20150225–116).

Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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