OPEN

Is a Preservation Solution for Living Donor Liver Transplantation Needed? Adding a New Chapter in LDLT!

Abdul Wahab Dogar, MBBS, FCPS,[1] Kaleem Ullah, MBBS, FCPS,[1] Shams-ud-din, MBBS, FCPS,[1] Syed Hasnain Abbas, MBBS, FCPS,[1] Azhar Hussain, MBBS, MD,[1] Abdul Ghaffar, MBBS, FCPS,[1] Hafiz Bilal, MBBS, FCPS,[1] Siraj-ud-din, MBBS, FCPS,[1] Azam Shoaib, MBBS, FCPS,[1] Bilal Ahmed, MBBS, FCPS, MS,[1] Hamid Raza, MBBS, FCPS,[1] Ameer Hamza, MBBS, FCPS,[1] Abu Bakar Hafeez Bhatti, MBBS, FRCS, FCPS,[2] Subash Gupta, MBBS, FRCS,[3] Sylvester M. Black, MD, PhD,[4] and Khalid Mumtaz, MBBS, MSc[5]

Background. Preservation solutions are required for organ viability in deceased donor liver transplantation (LT). However, their role in live donor LT (LDLT) has not been standardized. **Methods.** Eighty adult recipients who underwent right lobe LDLT at the Department of Liver Transplantation Surgery, Gambat, Pakistan, were studied. Based on shorter cold ischemia time and no back table reconstruction work, recipients were assigned to receive "no preservation solution" (cases/non–histidine-tryptophan-ketoglutarate group; n = 40) or "HTK group" (controls; n = 40). Early allograft dysfunction (bilirubin, transaminases, and international normalized ratio), postoperative complications (biliary and vascular), hospital stay, and 1-y survival were reported. The direct cost was also reported. **Results.** Demographics and clinical characteristics were comparable in the 2 groups. Comparing cases versus controls, mean bilirubin, alanine aminotransferase, aspartate aminotransferase, and international normalized ratio on postoperative day 7 were similar in the 2 groups. Five (12.5%) cases and 4 (10%) controls developed early allograft dysfunction ($P = 0.72$). Post-LT complications (biliary leak 2.5% in cases versus 0 in control), strictures (15% in cases versus 17.5% in controls), hepatic artery thrombosis (2.5% versus 00%), and portal vein thrombosis (0 versus 2.5%) were comparable. Mean hospital stay (10.80 + 2.36 and 11.78 + 2.91 d) and 30 d mortality (2.5% versus 5%) were also comparable. Finally, 1-y survival based on Kaplan-Meier analysis was comparable in both groups (ie, 92.5%; non-HTK group versus 90%; HTK group) ($P = 0.71$). The direct cost of using a non-HTK–based approach was less than the HTK solution. **Conclusion.** In a selected cohort of right lobe LDLT recipients, preservation solutions can be avoided safely with comparable outcomes.

(*Transplantation Direct* 2022;8: e1396; doi: 10.1097/TXD.0000000000001396).

INTRODUCTION

Organ preservation solutions have a vital role in solid organ transplantation.[1] During deceased donor organ procurement and transportation, donor organ metabolism is decreased and cellular injury is reduced by using a preservation solution.[2] The body of evidence supporting the use of organ preservation solutions in deceased donor liver transplantation (DDLT)[2] is substantial. However, the type of solution and its role in live donor liver transplantation (LDLT) are not well characterized in standardized guidelines.[3]

Preservation solutions differ in composition but share similar objectives of reducing graft edema, intracellular acidosis, and production of reactive oxygen species and help in providing energy substrates for metabolism.[2] Various preservation solutions and protocols are used with wide variability among the transplant centers. The most commonly used solutions are the University of Wisconsin (UW) and histidine-tryptophan-ketoglutarate (HTK). Despite their different compositions, both seem to be equally effective and safe in the long-term

Received 21 July 2022. Revision received 21 August 2022.
Accepted 25 August 2022.
[1] Pir Abdul Qadir Shah Jeelani Institute of Medical Sciences, Gambat, Sindh, Pakistan.
[2] Shifa international hospital, Islamabad, Pakistan.
[3] Max Speciality Hospital New Delhi, New Delhi, India.
[4] Division of Comprehensive Transplant Center, The Ohio State University, Wexner Medical Center, Columbus, OH.
[5] Division of Gastroenterology, Hepatology, and Nutrition, The Ohio State University, Wexner Medical Center, Columbus, OH.
The authors declare no funding or conflicts of interest.
A.H., A.W.D., and S.U.D. designed the study. A.G. collected and arranged data. S.H.A. and H.A.I. compiled data. A.H., S.D., K.U., and B.A. contributed to the statistical analysis of data and writing manuscripts. A.S., H.R., S.G., and A.H.S. contributed to writing the article. K.M. and S.M.B. provided supervision in the improvement of study design, data analysis, and article writing.
Correspondence: Azhar Hussain, MBBS, MD, Pir Abdul Qadir Shah Jeelani Institute of Medical Sciences, Gambat 66070, Pakistan. (azharhussain0139@gmail.com).

ISSN: 2373-8731
DOI: 10.1097/TXD.0000000000001396

preservation of the deceased donor graft.[3] In a meta-analysis by Feng et al,[4] 1200 patients were analyzed, and the outcomes of the 2 solutions were found comparable. Latchana et al[5] also concluded that UW and HTK solutions were similar in the majority of their outcomes. However, they demonstrated some benefits of HTK over UW, including lesser biliary complications and potential cost savings.

LDLT is the preferred option for liver transplantation (LT) in Asian countries with its specific advantages and disadvantages.[6] One of the advantages is shorter cold ischemia time (CIT).[7] This shorter CIT brings into question the use of preservation solutions in living donor grafts. Data on the use of preservatives in LDLT are limited, and one of the most extensive and recent studies from Mainland China compared the UW with HTK in a propensity-matched 106 pairs of patients. The outcomes in terms of biochemical labs, length of stay, and patient and graft survival were comparable in the 2 groups.[8] Testa et al[9] perfused 30 right LDLT grafts alternatively with UW and HTK solution. At a mean follow-up of 13 mo, no differences were found in the liver biochemistries, complications, and graft survival. Moreover, they found the use of HTK was less expensive than UW. Chan et al[10] and Ringe et al[11] also compared UW with HTK in a cohort of 30 patients each. Initial 30 grafts were perfused with UW and the subsequent 30 with HTK solution. Post-LDLT liver biochemistry, prothrombin time, and graft survival were comparable. They also found the cost of the HTK solution was lower.

In DDLT, the CIT is usually longer because of the transportation of a donor's allografts to the recipients' hospital at different locations. Also, a certain amount of bench work such as vascular reconstruction might be needed to enable expeditious implantation,[5] although, in LDLT, the donor and the recipient are in adjacent operating rooms, and graft anatomy is known before extracting the graft. Moreover, CIT is much shorter because the transit time between donor hepatectomy and implantation is minimal, and in some instances, back table reconstruction is also not needed. In this context, we hypothesize that using cold normal saline (NS) perfusion without any commercial preservation solution is feasible and safe in selected LDLT recipients. Therefore, we decided to compare the use of cold NS flushing with HTK perfusion in selected LDLT grafts.

MATERIALS AND METHODS

This prospective, case-control study was conducted from February 2020 to August 2020 at Pir Abdul Qadir Shah Jeelani Institute of Medical Sciences, Department of Liver Transplantation, Gambat, Pakistan. A study was conducted to determine the feasibility and safety of selected liver grafts flushed with cold NS and to compare their outcomes with grafts preserved in HTK solution. Right lobe liver donors and recipients were evaluated according to a standardized LDLT protocol published earlier.[12] During this study period, 80 adult recipients who underwent right lobe LDLT with only the right hepatic vein for reconstruction were studied. All these grafts were selected based on shorter CIT and did not need back table reconstruction. Based on the consecutive sampling technique, the first 40 adult recipients received a graft preserved using HTK solution (controls/HTK group: n = 40), and later, 40 adult recipients received a graft using only cold NS (cases/non-HTK group: n = 40).

Inclusion criteria for recipients were age ranging between 18 and 65 y, receiving right lobe grafts without MHV, MELD score >15, and HCC within UCSF criteria. All the recipients underwent detailed preoperative assessment by the primary team, including hepatologists, transplant surgeons, and anesthesiologists. Pulmonologists and cardiologists were also involved in specific assessments once deemed suitable by the primary team. Patients who needed multiple venous and portal reconstruction, acute liver failure and acute chronic liver failure recipients, dual-graft transplantation, transplant requiring jump graft for portal vein thrombosis (PVT), and candidates for re-LT were excluded from this study (Figure 1).

Live liver donor (LLD) evaluation included detailed history, physical examination, and thorough psycho-social assessment. Our center criteria used for donor selection include the age range of 18 to 40 y and body mass index <25 kg/m^2. LLDs were required to have no comorbid condition and an ABO blood group compatible with the recipient. Routine preoperative laboratory workup, favorable liver anatomy on dynamic tri-phasic CT scan, and magnetic resonance cholangio-pancreato-graphy were also performed. Donor liver anatomy, graft size and weight, future liver remnant, and graft to recipient weight ratio (GRWR) were calculated preoperatively. Donors with liver attenuation index >5, future liver remnant >30%, and GRWR ≥0.8 were selected.

Right hepatectomy was performed using our standard technique for LLD described previously.[12] An intraoperative cholangiogram was performed for all donors to delineate the biliary anatomy. Anatomic liver parenchymal transections of donors were done using water jet dissection or ultrasonic aspiration without vascular inflow occlusion. The right lobe was then removed, weighed, and perfused through the portal vein with HTK solution or cold NS (without preservative use).

For grafts that didn't need back table reconstruction before implantation, the time of graft retrieval from the donor was synchronized with recipient explant hepatectomy. The graft was placed in a bowl surrounded by ice. The portal vein was cannulated and perfused with 2 L of cold NS (0.9% sodium chloride) and taken to the recipient's operating room for implantation. This group was referred to as the "cases/non-HTK group." In "controls/HTK solution group" grafts were perfused with HTK solution as per routine. In these cases, the graft was immediately placed in an ice container and perfused with 2 L of HTK solution (Custodiol Bretschneider HTK solution, Germany). Anterior segment (segment V/VIII) venous reconstruction was not considered in cases with small caliber <5-mm segment V/VIII veins or having a small drainage area (Figure 2). It was planned on preoperative CT findings and confirmed operatively. At the time of implantation, the graft was perfused with 2 L of cold saline (0.9% sodium chloride) thoroughly to flush the HTK from the graft.

Recipient graft implantation was performed by standard piggyback technique. Intraoperative Doppler ultrasound was performed to confirm the vascular patency and flow. The biliary reconstruction was done with a duct-to-duct technique. A cholangiogram was performed after completing the biliary anastomosis to rule out any leakage and narrowing. Hemostasis was secured, the abdomen was closed over 2 Jackson-Prader drains, and finally, the patient was transferred to the ICU. The patient was kept intubated as per the intensivist assessment for 12 to 24 h. The patient was extubated the next morning after confirmatory Doppler ultrasound for vascular patency. Enteral

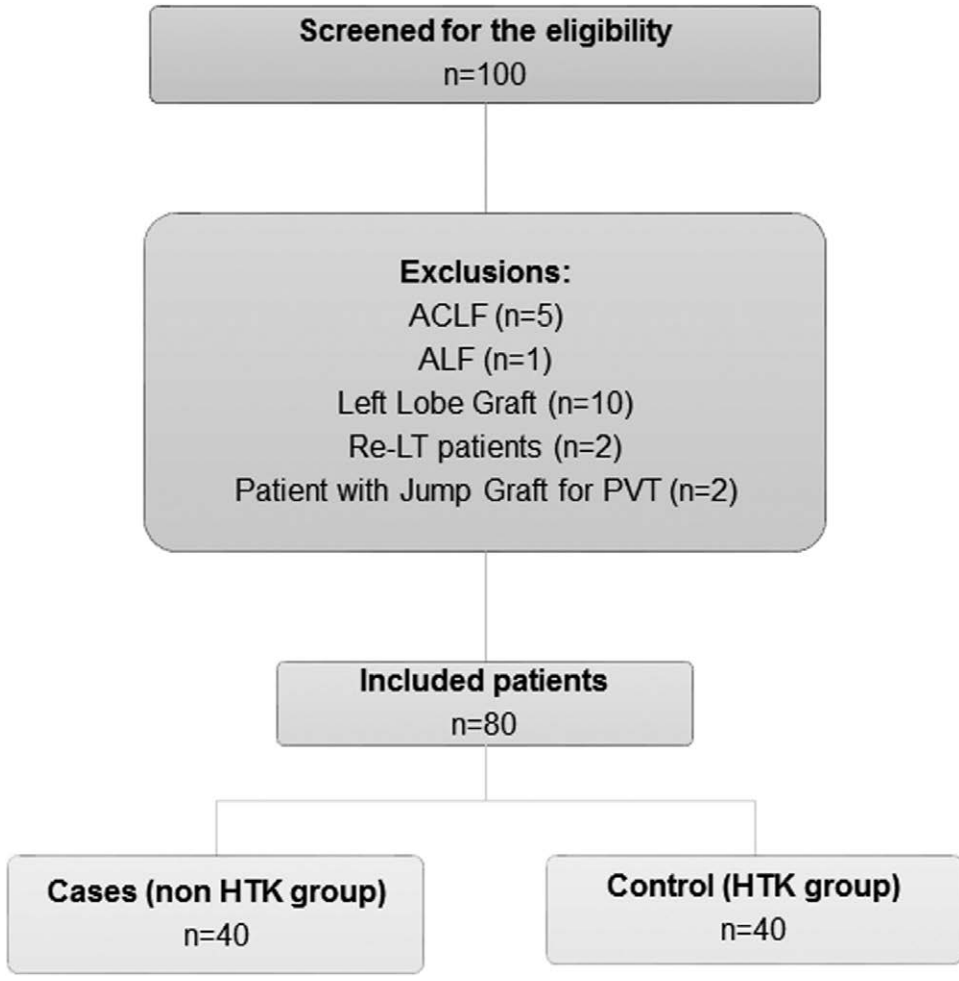

FIGURE 1. Study flow diagram of enrollment of patients in the study. HTK, histidine-tryptophan-ketoglutarate; LT, liver transplantation.

nutrition was usually started on the first postoperative day as soon as bowel sounds were audible

Intravenous methylprednisolone 500 mg was given as an induction immunosuppressant during the anhepatic phase. Prophylactic antibiotic coverage using intravenous piperacillin/tazobactam was given for 5 d. On the first postoperative day, intravenous methylprednisolone 100 mg was given daily to all recipients. Intravenous methylprednisolone was tapered to 80 mg, 60 mg, and then 40 mg on the second, third, and fourth postoperative days respectively, and finally switched to oral

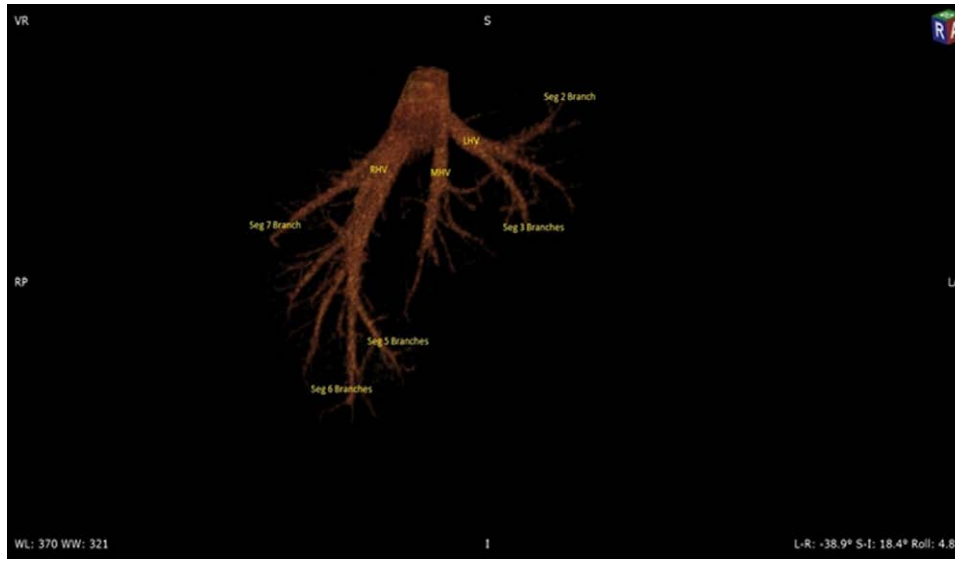

FIGURE 2. 3D reconstruction of graft in a patient with no need for back table reconstruction.

prednisone 20 mg daily on day 5. Later on, prednisolone was tapered over the next 3 mo while continuing oral tacrolimus according to blood level. Oral tacrolimus was started on the first postoperative day as maintenance immunosuppression with a dose of 0.5 mg BID, and the dose was gradually adjusted to maintain trough levels up to 8 to 10 ng/mL in the first 3 mo, 5 to 8 ng/dL between 3 and 6 mo, and finally around 5 ng/dL after that. Oral Septran DS (trimethoprim 80 mg + sulfamethoxazole 400 mg) on an alternate day and oral fluconazole 200 mg once a day were also continued for 3 mo.

Daily Doppler ultrasound was performed for the first 5 d to assess hepatic vasculature patency and flow. Postoperatively, daily complete blood count, liver function tests, creatinine, electrolytes, and prothrombin time with international normalized ratio (INR) were done for 7 consecutive days and then on alternate days until the patient was discharged from the hospital.

CIT was defined as the time from the flushing of the donor portal vein with preservative solution/cold NS until the removal of the graft from cold solution for implantation. And warm ischemia time (WIT) was defined as the time interval between graft removal from the preservation solution or cold NS until graft reperfusion.[13] Data on the recipients and donors were collected on predesigned data collection forms and maintained on computer-based software.

Outcomes and Follow-up

The primary outcome was to compare early allograft dysfunction (EAD) and primary nonfunctioning graft in the cases/non-HTK group (n = 40) versus "control/HTK group" (n = 40). The EAD was assessed by liver function tests, including bilirubin, transaminase, and INR from first postoperative to the seventh day. EAD was defined by the presence of >1 of the following on any postoperative day between 1 and 7: bilirubin >10 mg/dL, INR >1.6, and alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2000 IU/mL.[14] Primary nonfunctioning graft was defined as irreversible loss of graft function within the first 7 d characterized by AST >5000 IU/mL, INR >2, and acidosis.[15,16] The secondary outcomes included postoperative complications, such as biliary and vascular complications, and acute cellular rejection (ACR). Biliary complications included biliary leak and stricture assessed using magnetic resonance cholangio-pancreato-graphy + ERCP. Vascular complications included hepatic artery thrombosis (HAT), and PVT was assessed by using a Doppler ultrasound scan and confirmed with a tri-phasic CT scan. For ACR diagnosis, a liver biopsy was done. We also reported 30-d mortality and 1-y survival rate. Finally, the direct cost of comparing NS with preservation solutions (HTK) was reported.

After discharge, the patients were followed up for 1 y. Follow-up was performed weekly for the first month, biweekly for 3 mo, and then monthly until the end of the first year. Complete blood count, liver function tests, serum creatinine, and electrolytes levels were done on each follow-up visit. The ethical committee of our hospital approved the study.

Statistical Analysis

All quantitative variables were measured in terms of mean with SD and compared using the standard *t*-test. Categorical data were expressed as percentages and compared using the chi-square test and Fisher exact test. For the time-to-event analysis, the Kaplan-Meier survival curve was used by using 1-y survival or death as the endpoint. A P value of <0.05 was considered statistically significant.

Demographic data of donors and recipients and graft characteristics were collected. Data were compared between the 2 groups. Data including liver function tests, including total bilirubin, AST, ALT, INR, CIT, and WIT of the recipient at postoperative day 7 in both groups, were analyzed as quantitative variables with mean ± SD. Posttransplant complications such as HAT, PVT, biliary complications, ACR, and 30-d hospital mortality were analyzed as qualitative variables. SPSS, version 21, was used for statistical analysis. A P value of <0.05 was considered statistically significant.

RESULTS

Donor Demographics and Graft Characteristics

The mean age of donors in the non-HTK group and HTK group was 24.77 ± 5.90 y and 23.73 ± 6.13 y (P = 0.44), respectively. The majority in the non-HTK group were males (n = 23; 57.5%). Different variables such as donor age, gender, graft weight, blood loss, operative time, and hospital stay were comparable between the 2 groups (Table 1).

Recipients' Characteristics and Comparison With Case Group

Eighty LDLT recipients were included in the study, according to the inclusion criteria (Figure 1). The mean age of recipients in the non-HTK and HTK groups was 38.80 ± 9.70 and 37.63 ± 9.42 y, respectively. The majority of recipients were male in both groups (92.5% in non-HTK and 87.5% in the HTK group, P = 0.65). Viral hepatitis was the most common etiology of liver disease in both groups (n = 36; 90% in non-HTK and n = 37; 92.5% in the HTK group). More patients in the HTK group had HCC (n = 7; 17.5%) than in the non-HTK group (n = 4; 10%) (P = 0.51). The MELD-Na score in the non-HTK and HTK groups was comparable (20.20 ± 5.17 and 19.97 ± 5.54; P = 0.85). The majority of the recipients in both groups had a Child-Turcotte-Pugh score "C" (n = 31, 77.5% in the HTK and n = 33, 82.5% in the non-HTK group; P = 0.58) (Table 2).

CIT (5.03 ± 0.76 minutes versus 6.01 ± 0.68 min; P < 0.54) and WIT (24.58 ± 3.35 min versus 24.98 ± 2.30 min; P < 0.53) in the non-HTK group were comparable to the HTK group. Other intraoperative variables such as operation time, blood loss, and GRWR were also comparable in the 2 groups (Table 1).

TABLE 1.

Donor demographics and graft characteristic features

Variables	Non-HTK group (n = 40)	HTK group (n = 40)	P
Donor parameters			
Age (y)	24.77 ± 5.90	23.73 ± 6.13	0.44
Gender			0.65
Male	23 (57.5%)	21 (52.5%)	
Female	17 (42.5%)	19 (47.5%)	
BMI (kg/m^2)	20.83 ± 3.20	21.45 ± 2.98	0.37
LAI	8.08 ± 2.12	12.42 ± 3.44	<0.001
Graft weight (g)	700.00 ± 119.89	722.45 ± 120.43	0.40
Operation time (min)	384.450 ± 65.35	388.0 ± 53.59	0.79
GRWR	1.18 ± 0.41	1.10 ± 0.27	0.42
CIT (min)	5.03 ± 0.76	6.13 ± 0.68	0.54
WIT (min)	24.58 ± 335	24.98 ± 2.30	0.53

BMI, body mass index; CIT, cold ischemia time; GRWR, graft to recipient weight ratio; HTK, histidine-tryptophan-ketoglutarate; LAI, liver attenuation index; WIT, warm ischemia time.

TABLE 2.

Recipient demographics, clinical characteristics, and laboratory values

Variables	Non-HTK group (n = 40)	HTK group (n = 40)	*P*
Recipients			
Age (y)	38.80 + 9.70	3763 + 9.42	0.584
Gender			
Male	37 (92.5%)	35 (87.5%)	0.71
Female	3 (7.5%)	5 (12.5%)	
BMI (kg/m^2)	23.08 ± 4.67	22.28 ± 4.13	0.42
Etiology			
Viral	36 (90%)	37 (92.5%)	0.51
NASH	1 (2.5%)	1 (2.5%)	
Alcoholic	0 (0%)	0 (0%)	
Budd-Chiari syndrome	1 (2.5%)	0 (0%)	
PBC	0 (0%)	1 (2.5%)	
Wilson	2 (5%)	0 (0%)	
PSC	0 (00%)	1 (2.5%)	
HCC	4 (10%)	7 (17.5%)	0.51
Co-morbidities			
DM	3 (7.5%)	1 (2.5%)	0.61
HTN	0 (0%)	1 (2.5%)	1.00
CVD	0 (0%)	0 (0%)	0.00
CTP score			
A	2 (5%)	1(2.5%)	0.58
B	5 (12.5%)	8 (20%)	
C	33 (82.5%)	31 (77.5%)	
MELD-Na	20.20 ± 5.17	19.97 ± 5.54	0.85
Operation time (min)	537.25 ± 62.92	530.25 ± 66.58	0.63
Blood loss (mL)	1517.50 ± 315.32	1592.50 ± 272.11	0.25
Hospital stays (d)	10.80 ± 2.36	11.78 ± 2.91	0.10
Mean postoperative labs (at day 7)			
Total bilirubin (mg/dL)	2.68 ± 2.17	2.71 ± 2.46	0.95
INR (IU/L)	1.29 ± 0.10	1.51 ± 0.14	0.00
ALT (IU/L)	153.31 ± 92.81	180.67 ± 138.08	0.31
AST (IU/L)	103.97 ± 36.27	118.80 ± 136.77	0.58

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CTP, Child-Turcotte-Pugh; CVD, cardiovascular disease; HCC, hepatocellular carcinoma; HTN, hypertension; HTK, histidine-tryptophan-ketoglutarate; INR, international normalized ratio.

On postoperative day 7, laboratory data including mean ALT (153.31 ± 92.81 IU versus 180.67 ± 138.08 IU; *P* = 0.31), mean AST (103.97 ± 36.27 IU versus 118.80 ± 136.77; *P* = 0.58), and mean total bilirubin (2.68 ± 2.17 versus 2.71 ± 2.46; *P* = 0.95) in the non-HTK group were comparable to the HTK group (Table 2). On further comparison, ALT, AST, and INR between the 2 groups from day 1 to day 7 were also similar (Figure 3).

Primary Outcome

EAD was observed in 5 (12.5%) patients in the non-HTK as compared with 4 patients (10%) in the HTK group (*P* = 0.72).

Secondary Outcomes

Overall morbidity (Clavin-Dindo Grade >III complications) was comparable in the HTK (n = 12; 30%) and non-HTK group (n = 13; 32.5%) (*P* = 0.80). Postoperative complications including bile leak, biliary stricture, ACR, HAT, and PVT were also equivalent between the 2 groups. Only 1 (2%) patient had a bile leak and belonged to the non-HTK group.

Mean hospital stay in the non-HTK group (10.80 ± 2.36 d) was comparable to the HTK group (11.78 ± 2.91 d) (*P* = 0.10). One patient (2.5%) died at 30 d in the non-HTK group, whereas 2 (5%) died in the HTK group (Table 3). Kaplan-Meier analysis showed that 1-y post-LT survival rate for the non-HTK group (case group) and HTK solution group (control group) was 92.5% (10.65–12.00 mo) and 90% (10.62–11.97 mo), respectively (1-y post-LT log-rank *P* = 0.713) (Figure 4).

Direct Cost Analysis

We used 2 L of HTK solution for each patient in the HTK, and the direct cost of 1 L of HTK solution in Pakistan is $1000 (equal to 200 000 rupees) This means a total of $2000 (400 000 rupees) per patient. On the other hand, in the non-HTK group, we used cold NS. One L of cold NS solution costs only $0.5 (100 rupees). This means $1 (200 rupees) for each patient in the non-HTK solution. Therefore, using HTK solution compared with cold NS is much expensive and adds up to the total cost of the LDLT procedure.

DISCUSSION

Simple hypothermia might be sufficient for maintaining the organ viability for a shorter duration, but for longer preservation, various preservative solutions are used.[2] The need for preservative solutions in LDLT is not standardized in transplant centers. To our knowledge, this is the first innovative report on avoiding preservative solutions in LDLT recipients. We compared the non-HTK–based approach with the widely used HTK solution as a preservative in a specific cohort of our LDLT recipients. We found that EAD including liver function tests and postoperative complications (biliary and vascular), 30-d mortality, and 1-y survival were comparable in the 2 groups. We also found that avoiding the preservative solution has an impact on saving direct costs.

Preservative solutions used in DDLT were developed to maintain longer graft viability and extend CIT, making these solutions an inevitable component of the transplant procedure. Various preservative solutions used have their beneficial effect and some disadvantages.[17] UW solution, which is the most used solution during LT, contains hydroxyethyl starch, which induces aggregation of red blood cells, promoting occlusion and incomplete washout of blood during cold perfusion.[18,19] It had also been reported to be associated with significant arrhythmias and myocardial depression and even can lead to cardiac arrest because of high potassium content.[20] The second most commonly used preservative solution is the HTK solution. Testa et al[9] reported that HTK solution could lead to hypotension after reperfusion, especially in poor flushing of the graft. Therefore, avoiding the use of preservative solutions in LT, if not indicated, is justified and might protect the recipients from all these mentioned complications.

Preservative solutions are also used in LDLT, even though there are no standardized guidelines. The main purpose to use a preservative solution is to preserve the viability of graft during the CIT, which, in LDLT, is not a matter of major concern. CIT has a significant effect on primary graft function and is also a reliable predictor for graft survival.[21] The direct effect of the CIT on the graft is the release of cytotoxic metabolites causing damage to the hepatic sinusoidal epithelial cells, resulting in graft injury.[22,23] CIT should be minimized as much as possible to prevent morbidities and reduce the cost associated with a prolonged hospital stay.[24,25]

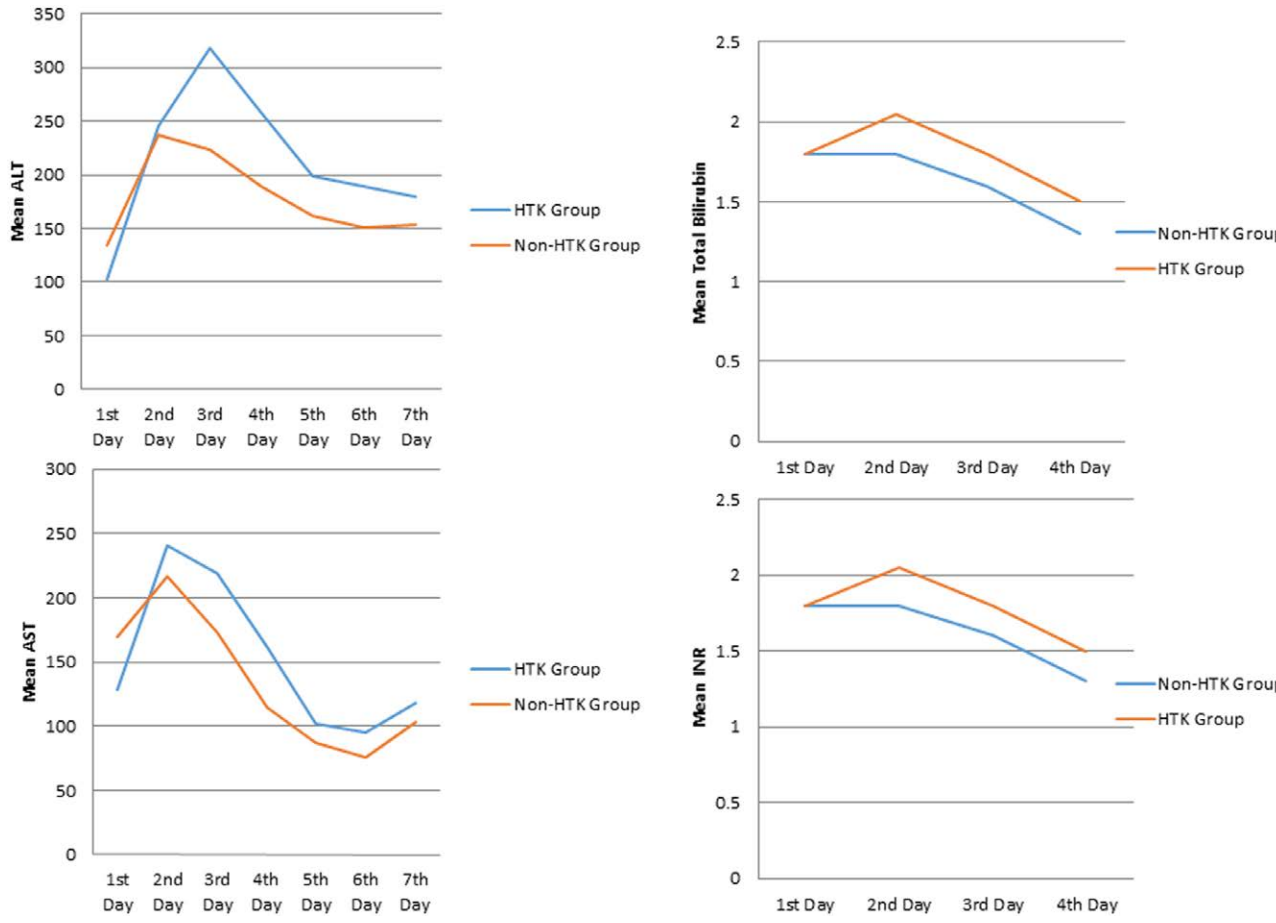

FIGURE 3. A, Comparison of mean postoperative ALT from day 1 to 7. B, Comparison of mean postoperative AST from day 1 to 7. C, Comparison of mean postoperative total bilirubin from day 1 to 4. D, Comparison of mean postoperative INR from day 1 to 4. ALT, alanine aminotransferase; AST, aspartate aminotransferase; HTK, histidine-tryptophan-ketoglutarate; INR, international normalized ratio.

TABLE 3.

Comparison of various outcomes in non-HTK and HTK groups.

Complication	Non-HTK group (n = 40)	HTK group (n = 40)	*P*
EAD	5 (12.5%)	4 (10%)	0.72
PNF	00 (00%)	1 (2.5%)	0.31
ACR	3 (7.5%)	4 (10%)	0.69
HAT	1 (2.5%)	0 (00%)	0.31
Sepsis	4 (10%)	5 (12.5%)	0.72
PVT	00	1 (2.5%)	0.31
Biliary complications			
Stricture	6 (15%)	7 (17.5%)	0.76
Leak	1 (2.5%)	00 (00%)	0.31
Clavin-Dindo Grade >III	12(30%)	13 (32.5%)	0.80
30-d mortality	1 (2.5%)	2 (5%)	0.72
1-y mortality (excluding first month)	02 (5%)	2(5%)	1.0

ACR, acute cellular rejection; EAD, early graft dysfunction; HAT, hepatic artery thrombosis; HTK, histidine-tryptophan-ketoglutarate; PNF, primary nonfunction; PVT, portal vein thrombosis.

In selected cases of LDLT, we did not need to perform back table reconstruction, and only cold NS solution for graft flushing may be justified (Figure 2). We compared the operative parameters of these cases with the HTK solution group (preservative in routine cases). We selected the appropriate candidates for nonpreservative solution use. It is reflected by significantly low CIT, reflecting that no back table vascular reconstruction was done.

We also compared the outcomes of grafts flushed with cold saline (non-HTK group) with the grafts flushed with HTK solution. Regarding the comparison of postoperative lab parameters, we found no significant difference in transaminase levels in the non-HTK group. Also, the mean bilirubin and INR values at the same point in time in this study were comparable in both groups without any statistical significance. Other outcome parameters like a total hospital stay and postoperative complications (vascular and biliary) were similar in the 2 groups without any statistical significance. We also found that 30-d mortality was equal in both groups, whereas the 1-y survival was better in the non-HTK group. We also demonstrated that, by using cold NS, there is a significant cost reduction in comparison to the HTK solution.

Regarding controversial biliary complications and the use of the preservative solution, we observed comparable rates of biliary stricture in both groups (15% in the non-HTK versus 17.5% in the HTK group, $P = 0.761$). Other studies have reported controversies about the role of preservative solutions in biliary complications. Studies by Karakoyun et al[26] and Heidenhain et al[27] reported an increased risk of biliary complications using the UW solution as compared with the HTK solution. However, other studies showed heterogeneous results and found that HTK solution was associated with an increased risk of biliary

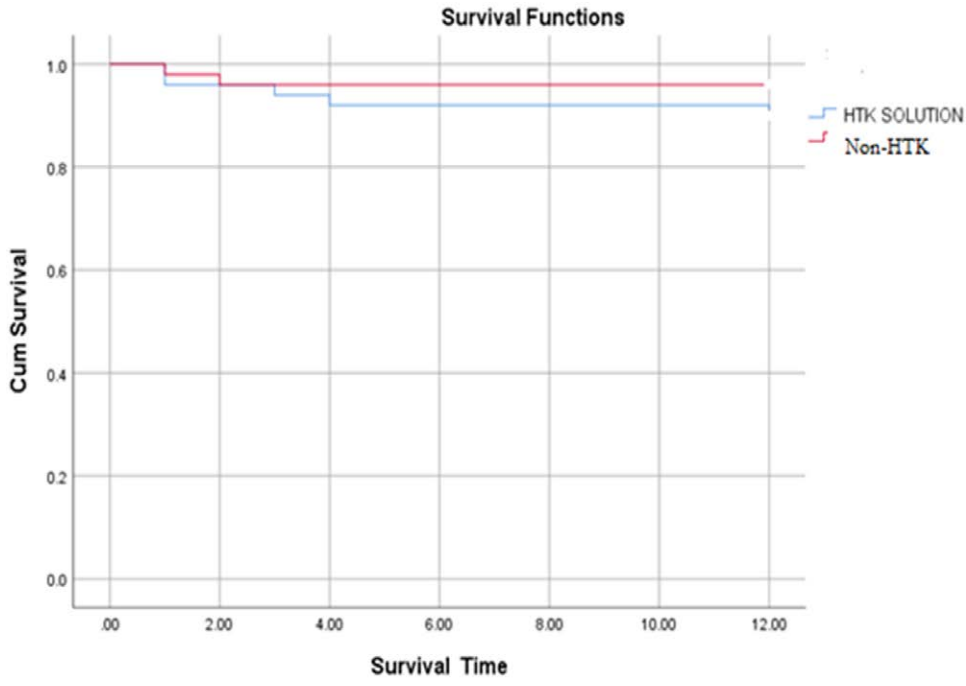

FIGURE 4. Kaplan-Meier showing comparable survival rate in non-HTK and HTK groups at 1 y postliver transplantation. Survival rate for the non-HTK group and HTK group was 92.5% (10.65–12.00 mo) and 90% (10.62–11.97 mo), respectively (*P* value = 0.71). HTK, histidine-tryptophan-ketoglutarate.

complications. They also reported overall increased morbidity in the HTK group.[28,29]

In our study, the postoperative complications and the overall 1-y survival rate in the nonpreservation group (92.5%) and the HTK group (90%) were equal and matched with other studies from the region.[30] These promising outcomes of our study clearly show that commercial preservation solutions are not mandatory and can be avoided in specific cases with the technique mentioned earlier, especially with low anticipated CIT.

Although these preservation solutions (UW solution and HTK solution) have been proven to be effective in preserving graft integrity and improving overall graft and recipient survival outcomes in the long term,[28,29] there are no data regarding cold NS as an alternative preservative solution for live liver grafts, which is a very cost-effective and readily available option. Though, the mechanistic effects of cold NS on grafts, especially its impact on the endothelium, meeting nutritional requirements of the graft, preventing oxidative damage, possible thresholds for CIT, and overall graft survival in LDLT are largely unknown. But from an economic perspective, we found that avoiding the use of preservation solutions is very attractive. It can save hospitals the direct costs of expensive preservation solutions for live donor liver transplant programs. This may be especially important for regions of the world where resources may be constrained.

There are a few limitations of this study. First, the sample size of this study is relatively small, and observed perioperative and survival outcomes may not be an actual representative of real-world outcomes. Second, the study groups were not randomized; rather, the consecutive sampling technique was used in this study, which may not confound true effects of cold NS on graft and recipient survival in a real-world setting in comparison to HTK solution. Third, the mean follow-up period for this study is about 1 y, which is not adequate to draw strict conclusions and recommend cold NS as a preservation solution in routine for LDLT. There is a need for well-designed prospective cohort studies or randomized controlled clinical trials and a larger sample size to validate our findings and add a new chapter to LDLT surgeries.

CONCLUSIONS

We are the first live donor liver transplant center to report that, in selected recipients, where back table reconstruction is not needed and CIT is reduced, the non-HTK or cold NS preservation approach is comparable to the HTK preservation solution. Avoiding commercial preservation solutions is safe with equivalent EAD, postoperative complications, and graft and patient survival. This approach is also found to reduce the cost of the use of preservative solution. Further prospective studies are needed to compare the nonpreservation solution approach to confirm our findings.

REFERENCES

1. Chen Y, Shi J, Xia TC, et al. Preservation solutions for kidney transplantation: history, advances and mechanisms. *Cell Transplant*. 2019;28:1472–1489.
2. Guibert EE, Petrenko AY, Balaban CL, et al. Organ preservation: current concepts and new strategies for the next decade. *Transfus Med Hemother*. 2011;38:125–142.
3. Upadhya GA, Strasberg SM. Glutathione, lactobionate, and histidine: cryptic inhibitors of matrix metalloproteinases contained in University of Wisconsin and histidine/tryptophan/ketoglutarate liver preservation solutions. *Hepatology*. 2000;31:1115–1122.
4. Feng L, Zhao N, Yao X, et al. Histidine-tryptophan-ketoglutarate solution vs. University of Wisconsin solution for liver transplantation: a systematic review. *Liver Transpl*. 2007;13:1125–1136.
5. Latchana N, Peck JR, Whitson BA, et al. Preservation solutions used during abdominal transplantation: current status and outcomes. *World J Transpl*. 2015;5:154–164.
6. Chen CL, Kabiling CS, Concejero AM. Why does living donor liver transplantation flourish in Asia? *Nat Rev Gastroenterol Hepatol*. 2013;10:746–751.

7. Thuluvath PJ, Yoo HY. Graft and patient survival after adult live donor liver transplantation compared to a matched cohort who received a deceased donor transplantation. *Liver Transpl*. 2004;10: 1263–1268.
8. Xu X, Zhu YF, Lv T, et al. Histidine-Tryptophan-Ketoglutarate solution versus University of Wisconsin solution in adult-to-adult living donor liver transplantation. A propensity score matching analysis from mainland China. *Medicine*. 2020;99(51):e23584.
9. Testa G, Malagó M, Nadalin S, et al. Histidine-tryptophan-ketoglutarate versus University of Wisconsin solution in living donor liver transplantation: results of a prospective study. *Liver Transpl*. 2003;9:822–826.
10. Chan SC, Liu CL, Lo CM, et al. Applicability of histidine-tryptophan-ketoglutarate solution in right lobe adult-to-adult live donor liver transplantation. *Liver Transpl*. 2004;10:1415–1421.
11. Ringe B, Braun F, Moritz M, et al. Safety and efficacy of living donor liver preservation with HTK solution. *Transpl Proc*. 2005;37:316–319.
12. Dogar AW, Uddin S, Ghaffar A, et al. Challenges of continuation of live liver donor programme during COVID-19 pandemic in Pakistan: outcomes and lessons learned. *BMJ Open Gastroenterol*. 2021;8:e000723.
13. Esquivel CO. Liver transplantation with donation after cardiac death: a treacherous field! Comment on "liver transplantation using organ donation after cardiac death". *Arch Surg*. 2011;146:1023.
14. Olthoff KM, Kulik L, Samstein B, et al. Validation of a current definition of early allograft dysfunction in liver transplant recipients and analysis of risk factors. *Liver Transpl*. 2010;16:943–949.
15. Hoyer DP, Paul A, Gallinat A, et al. Donor information based prediction of early allograft dysfunction and outcome in liver transplantation. *Liver Int*. 2015;35:156–163.
16. Bolondi G, Mocchegiani F, Montalti R, et al. Predictive factors of short term outcome after liver transplantation: a review. *World J Gastroenterol*. 2016;22:5936–5949.
17. Prasad GS, Ninan CN, Devasia A, et al. Is Euro-Collins better than ringer lactate in live related donor renal transplantation? *Indian J Urol*. 2007;23:265–269.
18. Morariu AM, Vd Plaats A, V Oeveren W, et al. Hyperaggregating effect of hydroxyethyl starch components and University of Wisconsin solution on human red blood cells: a risk of impaired graft perfusion in organ procurement? *Transplantation*. 2003;76:37–43.
19. Plaats A, 't Hart NA, Morariu AM, et al. Effect of University of Wisconsin organ-preservation solution on haemorheology. *Transpl Int*. 2004;17:227–233.
20. Moray G, Sevmis S, Karakayali FY, et al. Comparison of histidine-tryptophan-ketoglutarate and University of Wisconsin in living-donor liver transplantation. *Transpl Proc*. 2006;38:3572–3575.
21. Totsuka E, Fung JJ, Lee MC, et al. Influence of cold ischemia time and graft transport distance on postoperative outcome in human liver transplantation. *Surg Today*. 2002;32:792–799.
22. Clavien PA, Harvey PR, Strasberg SM. Preservation and reperfusion injuries in liver allografts. An overview and synthesis of current studies. *Transplantation*. 1992;53:957–978.
23. Kang KJ. Mechanism of hepatic ischemia/reperfusion injury and protection against reperfusion injury. *Transpl Proc*. 2002;34:2659–2661.
24. Pan ET, Yoeli D, Galvan NTN, et al. Cold ischemia time is an important risk factor for post-liver transplant prolonged length of stay. *Liver Transpl*. 2018;24:762–768.
25. Belzer FO, Southard JH. Principles of solid-organ preservation by cold storage. *Transplantation*. 1988;45:673–676.
26. Karakoyun R, Romano A, Nordström J, et al. Type of preservation solution, UW or HTK, has an impact on the incidence of biliary stricture following liver transplantation: a retrospective study. *J Transpl*. 2019;2019:8150736.
27. Heidenhain C, Pratschke J, Puhl G, et al. Incidence of and risk factors for ischemic-type biliary lesions following orthotopic liver transplantation. *Transpl Int*. 2010;23:14–22.
28. Meine MH, Zanotelli ML, Neumann J, et al. Randomized clinical assay for hepatic grafts preservation with University of Wisconsin or histidine-tryptophan-ketoglutarate solutions in liver transplantation. *Transpl Proc*. 2006;38:1872–1875.
29. Gulsen MT, Girotra M, Cengiz-Seval G, et al. HTK preservative solution is associated with increased biliary complications among patients receiving DCD liver transplants: a single center experience. *Ann Transpl*. 2013;18:69–75.
30. Narasimhan G. Living donor liver transplantation in India. *Hepatobiliary Surg Nutr*. 2016;5:127–132.