Original Article Alleviating graft injury during liver transplantation by improving retrograde perfusion in standard orthotopic liver transplantation

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Abstract: This study aimed to explore the influence of improved retrograde perfusion in standard orthotopic liver transplantation on graft injury during surgery. Twenty-one patients who had undergone an improved method of retrograde perfusion in standard orthotopic liver transplantation comprised the experimental group, and 21 patients in the same period who had undergone the perfusion method in standard orthotopic liver transplantation comprised the control group. The results of the liver function tests in the two groups were compared after transplantation. In 21 patients, the time before inferior vena cava opening (T1), right inferior vena cava (RIVC) blood retrograde perfusion, and bleeding of 10 (T2), 50 (T3) and 200 mL (T4) from the portal vein, respectively, were recorded. Blood from the RIVC at T1, and donor hepatic portal vein blood at T2, T3, and T4, were extracted for biochemical testing and blood gas analysis, in order to compare changes in venous blood pH, PaCO,, PaO,, base excess of extracellular fluid (BEecf), HCO,, T-CO,, SaO,, alanine aminotransferase (ALT), gamma glutamyltransferase (GGT), K⁺, alkaline phosphatase (AKP) and aspartate aminotransferase (AST) at different times. The differences between the two groups in levels of AKP, total bilirubin (TBil), ALT, GGT, and AST after surgery were statistically significant (P<0.05). The pH, PaCO₂, PaO₂, BEecf, HCO₂, T-CO₂, and SaO₂ levels in the blood gas analysis demonstrated various fluctuations at T2 and T3, as well as significant differences between T1 and T4 (P<0.05). The HCO₂ and T-CO₂ values at T4 eventually returned to T1 levels (P>0.05), while the pH, PaO₂, BEecf, and SaO₂ levels were higher than those at T1 (P<0.05). The PaCO_a levels at T4 were lower than those at T1 (P<0.05). The biochemical test results indicated that the ALT, AST, AKP, and K⁺ from T1 to T4 all increased to their highest levels at T2, and declined to the lowest level at T4, but were still higher than those at T1. The differences in levels between any two points were statistically significant (P<0.05). The GGT levels increased at T2 and T3, and again decreased at T4 to levels that were lower than those at T1. The differences between T1 and T2, as well as between T3 and T4, were statistically significant (P<0.05), while the differences between T1 and T4 were not statistically significant (P>0.05). RIVC blood retrograde perfusion to the donor liver can rapidly reduce ischemia-reperfusion injury in standard orthotopic liver transplantation.

Keywords: Orthotopic liver transplantation, liver disease, improved method of retrograde perfusion, portal vein, blood, biochemistry

Introduction

In orthotopic liver transplantation (OLT), graft ischemia-reperfusion not only prevents recovery of normal tissue and organ function, but also aggravates dysfunction and structural damage induced by ischemia-reperfusion injury (IRI) [1]. Hepatic ischemia-reperfusion injury (HIRI), which causes a receptor internal environment disorder, electrolyte abnormalities, and severe acid-base imbalance, is difficult to avoid. HIRI has a major influence on postoperative primary graft nonfunction and biliary complications [2, 3]. The search for alternative methods to alleviate graft IRI through improved surgical technique is a focus of ongoing research in liver transplantation. In 1963, Starzl et al. [4, 5] performed the world's first standard orthotopic liver transplantation (SOLT), which has gradually been replaced by portal vein perfusion, due to greater difficulty in anastomosis of the hepatic artery than of the

Index	Control group (n=27)	Experimental group (n=27)	Р
Year	48.56±9.8	46.63±9.0	>0.05
Operation time (h)	8.11±0.69	8.01±0.7	>0.05
Percentage of hepatic steatosis (%)	23.6±3.02	24±4	>0.05
Cold ischemia time (h)	9.71±1.15	9.59±1.6	>0.05
Hot ischemia time (min)	5.33±3.23	5.39±3.1	>0.05
Primary disease			
Hepatocellular carcinoma	7	8	
Liver cirrhosis	13	10	>0.05
Hepatic failure	7	9	
PT (s)	14.3±2.15	14.83±3.5	>0.05
PT-INR	1.23±0.19	1.28±0.27	>0.05
Total protein (g/L)	64.56±10.9	64.38±13.1	>0.05
Albumin (g/L)	33.11±6.15	33.03±7.07	>0.05
Alkaline Phosphatase (U/L)	102.96±18.9	109.4±27.27	>0.05
Alanine aminotransferase (U/L)	42 (26-61)	46 (30-87)	>0.05
Aspertate aminotransferase (U/L)	84 (52-149)	56 (36-100)	>0.05
Glutamyl transpeptidase (U/L)	80 (35-204)	46 (29-90)	>0.05
Total bilirubin (µmol/L)	26 (17-189)	42 (24-290)	>0.05

 Table 1. Basic information of the control group and experimental group

Note: the difference was statistically significant, P<0.05.

portal vein, as well as the longer operation time and anhepatic phase. In 2003, Kniepeiss et al. [6] first reported that the initial graft function might potentially improve if inferior vena cava (RIVC) retrograde perfusion is used in piggyback liver transplantation. Despite subsequent progress in the surgical technique, initial graft dysfunction occurs in 20%-30% of patients postoperatively, and severe cases may develop primary graft nonfunction [7, 8]. There are few studies on the effects of improved retrograde perfusion, a new operative method, on graft IRI during SOLT. In this research study involving 21 patients, we explored the influence of improved retrograde perfusion on graft injury in SOLT, based on analysis of blood gas and biochemical changes in the RIVC and hepatic portal vein after retrograde perfusion with RIVC blood during the new liver phase.

Materials and methods

General information

Among 21 patients who had undergone OLT from September 2013 to December 2014 (16 males and 5 females, aged 23 to 69 years), 6

had been diagnosed with acute and severe chronic hepatitis, 9 with post-hepatitis B cirrhosis, and 6 with liver cancer. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Fujian Medical University. Written informed consent was obtained from all participants. In the control group, 21 patients in the same period had undergone the perfusion method in SOLT. The data are shown in Table 1.

Donor liver procurement

University of Wisconsin solution (UW) was used in liver transplantation for all 21 patients. The liver and kidney were cut rapidly and

concurrently, with dual perfusion established through the abdominal aorta and portal vein. The donor liver was kept in 4°C UW solution after removal. Before liver transplantation, routine pathologic examination of a rapid-frozen section should be performed to determine the amount of fatty degeneration in the donor liver. Fatty degeneration of less than 30% in the donor liver is considered the standard for liver transplantation.

Improved retrograde perfusion in SOLT

During liver transplantation, 1,000 mL of plasma was perfused in 21 patients via the hepatic portal vein catheter. After donor liver procurement, a catheter was imbedded in the portal vein during liver repair for use during operative plasma perfusion and sampling, with an average intraoperative blood transfusion of 2,500±200 mL. Improved retrograde perfusion in SOLT involves matching of the supra- and infrahepatic RIVC of the donor and receptor, which are opened before portal vein matching, to allow retrograde perfusion from the vena cava to the donor liver. The hepatic portal vein is blocked after bleeding 200 mL, and the por-

Index	Group	Time				
		Preoperation	First day after	Third day after	Fifth day after	Seventh day
	0	44.0.045				
PI (s)	Control group	14.3±2.15	15.54±2.03	13.37±1.63	12.59±1.89	12.42±1.32
	Experimental group	14.83±3.5	14.97±2.34	12.89±1.83	12.63±1.71	11.89±0.98
Total protein (g/L)	Control group	64.56±10.9	49.22±8.05	49±6.13	51.1±6.13	52.7±6.15
	Experimental group	64.38±13.1	51.04±9.86	51.7±7.44	52.2±7.4	54.56±4.58
Albumin (g/L)	Control group	33.11±6.15	22.78±4.01	24.3±4.45	27.37±4.6	30.92±3.51
	Experimental group	33.03±7.07	25.1±6.01	26.26±2.6	29.11±2.6	32.15±3.5
Alkaline Phosphatase (U/L)	Control group	102.96±18.9	74.67±16.87	75.59±18.84	83.74±18.82	95.11±27.08
	Experimental group	109.4±27.27	63.18±11.65*	65.6±16.7*	70.96±16.3*	76.62±12.37*

Table 2. Two groups of patients with four indicators in different time before and after surgery $(\bar{x}\pm s)$

Note: compared with control group, *P<0.05.

tal vein and hepatic artery are subsequently matched in sequence and opened. The control group used the perfusion method in SOLT, with the portal vein, the inferior vena cava, and the hepatic artery opened in sequence.

Index measurement

Changes in liver function on the first, third, fifth, and seventh day after transplantation were evaluated in both groups. The experimental group underwent OLT with improved retrograde perfusion. A sample was removed using a 10 mL syringe, which was used to abstract RIVC blood from the receptor. When the hepatic portal vein in the donor liver was opened after being fully perfused by retrograde RIVC blood, an empty syringe was used to obtain a sample after bleeding from the catheter in the hepatic portal vein (being careful to avoid trapping of air during sampling). The time point immediately before (T1) and after RIVC opening, the time point of RIVC blood retrograde perfusion and bleeding of 10 mL from the hepatic portal vein (T2), the time point immediately after RIVC blood retrograde perfusion and bleeding of 50 mL from the hepatic portal vein (T3), and the time point immediately after RIVC blood retrograde perfusion and bleeding of 200 mL from the hepatic portal vein (T4), were all recorded. We extracted RIVC blood from the receptor at T1 and from retrograde perfusion at T2, T3 and T4, which was perfused with RIVC blood to the hepatic portal vein. We conducted biochemical tests and blood gas analysis on the samples and compared the changes in venous blood pH, PaCO₂, PaO₂, base excess of extracellular fluid (BEecf), HCO3, T-CO2, SaO2, alanine aminotransferase (ALT), gamma-glutamyltransferase

(GGT), K⁺, alkaline phosphatase (AKP), and aspartate aminotransferase (AST) at different time points. The laboratory of the Fuzhou General Hospital of the Nanjing Military Area Command performed automated analysis of samples using i-STAT1 (Abbott, Chicago, IL, USA) and a fully automated biochemical analyzer, OLYMPUS AU2700 (Beckman Coulter, Pasadena, CA, USA).

Statistical analysis

Data were analyzed using SPSS 18.0 statistical software. Quantitative data of normal or approximately normal distribution were described using the mean \pm standard deviation ($\overline{x}\pm s$), while quantitative data of abnormal distribution were described using the median and interquartile range. The comparison of means between the two groups was performed using the t-test, the median was calculated from the nonparametric Mann-Whitney U test, and the chi-square test was used for qualitative data. Statistical analysis of the normally distributed data was conducted by analysis of variance of the randomized block design information, and any two values were compared using the Least Significant Difference method. Statistical analysis of abnormally distributed data was conducted using the Friedman method, with multiple-sample comparisons in a randomized block design. A P-value of <0.05 indicated statistical significance.

Results

Comparisons in recovery of liver function (normal distribution data) between the two groups at different times after surgery are shown in

Table 3. Two groups ofinterquartile range)	f patients with fou	r indexes at	different tim	e pre and pos	st-operation	(median,	
Index	Group		Time				
		Preoperation	First day after	Third day after	Fifth day after	Seventh day	

		Drooporation	First day after	Third day after	Fifth day after	Seventh day
		Freuperation	operation	operation	operation	after operation
Alanine aminotransferase (U/L)	Control group	42 (26-61)	734 (336-786)	511 (233-833)	320 (155-622)	200 (157-453)
	Experimental group	46 (30-87)	556 (450-1447)*	325 (168-428)*	142 (98-212)*	138 (73-227)*
Aspertate aminotransferase (U/L)	Control group	84 (52-149)	537 (247-902)	164 (82-423)	113 (63-232)	95 (69-161)
	Experimental group	56 (36-100)	318 (175-612)*	86 (55-120)*	66 (54-110)*	66 (35-102)*
Glutamyl transpeptidase (U/L)	Control group	80 (35-204)	113 (91-150)	93 (72-121)	100 (83-133)	117 (75-186)
	Experimental group	46 (29-85)	84 (57-144)*	73 (55-95)*	78 (66-113)*	97 (65-125)*
Total bilirubin (µmol/L)	Control group	26 (17-189)	72 (48-146)	53 (35-117)	64 (43-123.5)	76.2 (30-127)
	Experimental group	42 (24-290)	54 (30-75)*	44 (23-54)*	42 (21-57)	39 (20.7-55)*

Note: compared with control group, *P<0.05.

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Index	T1	T2	T3	T4
pН	7.34±0.07	6.8±0.15 [×]	6.86±0.17*	7.19±0.16 ^{%,*,#}
PaCO ₂ (mmHg)	41.26±5.92	97.64±12.98*	92.87±18.64*	77.41±12.59 ^{×,*,#}
PaO ₂ (mmHg)	63.05±11.66	34.05±7.88 ^{**}	30.9±10.17*	47±9.97 ^{**,*,#}
BEecf (mmol/L)	-4.05±2.18	-16.62±4.02 ^{**}	-13.24±4.88 ^{×,*}	-8.81±2.96 ^{×,*,#}
HCO ₃ ⁻ (mmol/L)	21.41±1.34	17.88±2.47*	19±2.52 [*]	20.98±1.56 ^{*,#}
T-CO ₂ (mmol/L)	23.62±1.66	19.71±2.63 ^{**}	20.95±2.62 ^{**}	23.95±1.36 ^{*,#}
SaO ₂ (%)	88.76±4.13	31.58±12.59 [%]	25.43±8.9 ^{×,*}	40.29±10.29 ^{%,*,#}

Notes: **Means statistical significance compared with T1 (P<0.05). *Means statistical significance compared with T2 (P<0.05). *Means statistical significance compared with T3 (P<0.05).

 Table 2. The AKP in the experimental group was
 significantly lower than in the control group (P<0.05) on the first, third, fifth, and seventh day after surgery; the differences between the two groups in prothrombin time (PT), total protein (TP), and albumin (ALB) showed no statistical differences (P>0.05) on the first, third, fifth, and seventh day after surgery. The comparison between the two groups in recovery of liver function (non-normal distribution data) at different times after surgery is shown in Table 3. The levels of total bilirubin (TBil), ALT, GGT, and AST in the experimental group were significantly lower than those in the control group (P<0.05) on the first, third, fifth, and seventh day after surgery.

After matching of the supra- and infra-hepatic RIVC and opening of the RIVC, the time from retrograde perfusion of the blood from the RIVC until bleeding of 200 mL from the donor liver was recorded at an average of 5 ± 3.1 min. The pH, PaCO₂, PaO₂, BEecf, HCO₃, T-CO₂, and SaO₂ in venous blood gas analysis of 21 patients demonstrated statistically significant differenc-

es (P<0.05), with large fluctuations at T2 and T3, compared with values at T1 and T4, respectively. The values at T4 tended to return to previous T1 levels. The HCO3 and T-CO2 values at T4 returned to T1 levels without statistically significant differences (P>0.05). For the pH, PaO, BEecf, and SaO₂ values, the T4 levels were higher than those at T1, with statistically significant differences (P<0.05). The PaCO₂ at T4 was also lower than at T1, with statistically significant difference (P<0.05, Table 4). Blood samples demonstrated elevations in the ALT, AST, AKP, and K⁺ levels from T1 to T4; all values reached highest levels at T2, before gradually declining to lowest values at T4. Nevertheless, the T4 values were higher than those at T1. The differences between any two points at the T1, T2, T3, and T4 time points were statistically significant (P<0.05). The GGT levels increased at T2 and T3, and then decreased at T4 to values that were even lower than those at T1. The differences between T1 and T2 as well as T3 and T4 were statistically significant (P<0.05), while those between T1 and T4 were not statistically significant (P>0.05; Tables 5, 6).

Index	T1	T2	ТЗ	T4
Alanine Aminotransferase (U/L)	59±22.31	1532±475 [*]	1066.3±278.7 ^{×,*}	781.14±231 ^{%, *,#}
Glutamyl Transpeptidase (U/L)	41±14.79	51.43±11.09 [*]	51.24±12.95 [*]	41.1±13.37 ^{*,#}
K⁺ (mmol/L)	4.47±0.59	9.24±1.37*	8.1±2.17 ^{×*,*}	5.8±2.16 ^{%,*,#}

Table 5. Values of 3 biochemical indexes under different data processing $(\bar{x}\pm s)$

Notes: **Means statistical significance compared with T1 (P<0.05). *Means statistical significance compared with T2 (P<0.05). *Means statistical significance compared with T3 (P<0.05).

 Table 6. Values of 2 biochemical indexes under different data processing (median and interquartile range)

Index	T1	T2	ТЗ	T4
Alkaline Phosphatase (U/L)	99 (72.5-150)	162 (131-168)**	145 (112-179) ^{*,*,#}	115 (104-132) ^{%,*,#}
Glutamic Oxalacetic Transaminase (mmol/L)	111 (57-139)	963 (715-1607)*	861 (610-1612) ^{**,*}	452 (338-1077) ^{**,*,#}

Notes: ^{**}Means statistical significance compared with T1 (P<0.01). *Means statistical significance compared with T2 (P<0.05). [#]Means statistical significance compared with T3 (P<0.05).

Discussion

Liver transplantation is now acknowledged worldwide as a common and effective means for the treatment of end-stage liver diseases. In particular, it is the best treatment option for acute liver failure (ALF). Currently, it has become the most effective means of treatment of primary liver cancer (PHC) [9]. However, liver transplantation is accompanied by major surgical trauma and obvious internal environmental disturbances, the most prominent of which is HIRI, which is difficult to avoid during liver transplantation. Since 1963, when Starzl et al. [4, 5] performed the world's first SOLT, development of methods to alleviate HIRI and improve intraoperative hemodynamics is among the major goals of liver transplantation research. In 1989, Tzakis et al. [10] first reported the piggyback technique of orthotopic liver transplant (PB-OLT), which is a surgical method used to overcome unstable hemodynamics during SOLT and retains smooth reflux in the RIVC in the anhepatic phase without venovenous bypass (VVBP). This prevents potential complications caused by VVBP. However, these techniques are still unable to solve the major problems of liver transplantation, which include HIRI and its major influence on postoperative primary graft nonfunction, as well as biliary, pulmonary, and nephritic complications.

In clinical liver transplantation, positive hepatic perfusion is generally used, particularly after matching of the supra- and infrahepatic RIVC and portal vein. This is also used for the portal

vein opening and before RIVC opening. Since the donor liver undergoes the injury process of cold ischemia, rewarming, warm ischemia, and reperfusion in sequence. IRI is difficult to avoid. and is a more serious and complicated problem than injury caused by simple ischemia. IRI of the graft is an important factor that results in postoperative hepatic dysfunction, and even results in primary graft nonfunction in serious cases. In 2003, Kniepeiss et al. [6] first reported that initial graft function may be improved if retrograde perfusion is used in PB-OLT. Recent research by Wagner et al. [11] showed that retrograde perfusion in SOLT may largely alleviate hepatic IRI compared with positive perfusion, and can protect liver function better, thus improving success and survival rates of transplantation. However, during retrograde perfusion in liver transplantation, hepatic metabolite reflux caused by portal vein opening will result in injury to the donor liver and body. Research on the possibility of reducing harmful hepatic metabolite reflux and further reduction in graft IRI is rarely reported. In this research study, we compared the application of improved retrograde perfusion via RIVC in SOLT such that the harmful metabolites released during hepatic ischemia-reperfusion are appropriately discharged, along with the systemic circulation of the receptor, in order to explore the influence of improved retrograde perfusion in SOLT on graft injury.

As shown in **Table 4**, the pH, BEecf, SaO₂, PaO₂, HCO_3^{-1} , and T-CO₂ levels at T2 and T3 are significantly lower than those at T1, while the PaCO₂

level increased significantly compared to that at T1. The differences in these values were statistically significant (P<0.01). Data fluctuate widely at T2 and T3, and values at T4 tend to return to previous levels at T1. The differences between values at T2 and T3 and those at T4 are statistically significant (P<0.05). The BEecf value declined to the lowest level at T2, then gradually increased and leveled off at T4, but was still lower than at T1. The differences between any two points among T1, T2, T3, and T4 were statistically significant (P<0.05). The SaO, varied widely at T2 and T3. The difference between the SaO, levels at T2 and T3 was statistically significant (P<0.05). In our research, the RIVC blood was perfused in a retrograde manner to the liver during transplantation after the portal vein of the donor liver bleeds about 200 mL. The differences in blood gas values at T1, T2, T3, and T4 showed improved retrograde perfusion. After matching with the open supraand infrahepatic RIVC, retrograde perfusion of the donor liver occurs after bleeding of the RIVC and the portal vein of the donor. The process enables the donor liver, with cold ischemia, low metabolism, and held in cold UW solution, to recover metabolic function. We dynamically observed that SaO, after hepatic retrograde perfusion declines most significantly at bleeding of 50 mL (T3), and is improved at bleeding of 200 mL (T4). This indicated that with retrograde perfusion of RIVC blood, the metabolism and oxygen consumption of the donor liver increase, most significantly at T3. As the retrograde perfusion of RIVC blood increases, oxygen consumption of the donor liver reduces at T4. We observed changes in pH, BEecf, HCO, T-CO₂, and PaCO₂, and found that the concentration of acid metabolites increased at T2 and T3, and declined at T4 with improved pH, as retrograde perfusion of RIVC blood increased. It is obvious that with retrograde perfusion of blood in the RIVC to the donor liver, acid metabolites are deposited during hepatic ischemia-reperfusion. Blood from the hepatic portal vein can discharge acid metabolites that have been deposited by metabolism.

Tables 5 and **6** show that levels of ALT, AST, AKP, and K^+ from T1 to T4 all rise to the highest point at T2, then gradually decline to the lowest point at T4, but are still higher than the levels at T1. The differences between any two points among T1, T2, T3, and T4 are statistically sig-

nificant (P<0.05). The GGT rises at T2 and T3, declines at T4, and is lower than the levels at T1. The differences between T1 and T2 as well as T3 and T4 are statistically significant (P<0.05), but the differences between T1 and T4 are not statistically significant (P>0.05). Blood biochemical examination at T1, T2, T3, and T4 demonstrated changes in ALT, AST, AKP, and GGT levels. Improved retrograde perfusion of blood in the RIVC to the donor liver results in cold ischemia and low metabolism. Once the liver is held in cold UW solution, it begins to recover metabolic function. After retrograde perfusion of the donor liver, the ALT, AST, AKP, and K⁺ rise significantly, particularly at T2. The levels begin to recover at T3 and recover significantly at T4. During liver transplantation, rewarming ischemic injury of new liver may occur due to the rising temperature of the donor liver. Strasberg et al. [12] believed that rewarming ischemic injury is the most important risk factor that results in initial graft dysfunction. Rewarming ischemic injury may result in the rise of AST and the low graft survival rate after liver transplantation. If the anhepatic phase lasts more than 90 minutes, serum AST, ALT, and hyaluronic acid rise significantly [13]. In this research study, functional injury of the donor liver is obvious after the IRI process. The injury is most obvious at T2, with beginning of recovery at T3 and obvious recovery at T4. If the metabolites and high K⁺ are not discharged, reflux will result in receptor electrolyte disorders and functional injury to important organs and the graft. This research study demonstrates improved retrograde perfusion of IVI blood after 200 mL are bled from the hepatic portal vein and the metabolites from hepatic ischemia-reperfusion are discharged, resulting in significant recovery of GGT, ALT, AST, and K⁺ levels at T4. This shows that reinjury of graft function caused by metabolites deposited during hepatic ischemia-reperfusion or electrolyte disturbances, and functional injury of important organs due to their entrance into the systemic circulation, can be reduced after bleeding from the hepatic portal vein.

In liver transplantation, HIRI is difficult to avoid. With the disruption of oxygen and nutrient supply during ischemia, energy reserves drop, and metabolites are deposited. Deficient ATP may lead to an imbalanced electrolyte concentration gradient inside and outside of the cell as

well as excess calcium in the mitochondria. These calcium ions further activate enzymes such as phospholipase, protease, and nuclease, resulting in cell apoptosis and necrosis. Since the activation of calpains results in the conversion of xanthine dehydrogenases (XD) into xanthine oxidases (XO), after reperfusion, a large number of hypoxanthines are converted to trioxypurines by XO. Since a large number of oxygen radicals are released, this becomes one of the causes for graft dysfunction [14]. In addition, microcirculation disturbances, activation of Kupffer cells, adhesion and aggregation of neutrophils, and the release of inflammatory cytokines after reperfusion may lead to further functional injury of the graft [15, 16]. The most prominent problems are acidosis and hyperkalemia [17, 18].

In this research study, improved retrograde perfusion is established based on retrograde perfusion, during which harmful metabolites generated in graft ischemia-reperfusion are discharged and 200 mL are bled from the portal vein. To improve retrograde perfusion intraoperatively during the first stage, the donor liver is lavaged with plasma in order to discharge the high K⁺ and acidosis metabolites generated in hepatic ischemia. Before retrograde perfusion in transplantation, performing hepatic lavage using 1,000 mL of plasma reduces the high K⁺ to normal physiological levels with the discharge of hepatic metabolites by anaerobic metabolism and acidosis. Further research is needed in order to determine whether the ideal condition is achieved. The K⁺ in the portal vein blood rises after the retrograde perfusion of the blood in the RIVC to the donor liver, gradually decreases after reaching the highest level at T2, and eventually returns to the lowest levels at T4. In theory, discharging more blood from the hepatic portal vein can reduce the high K⁺ level to its normal physiological state. Based on our previous experience, bleeding of more than 250 mL resulted in various hemodynamic fluctuations and unstable blood pressures. The urine volume decreased significantly with the administration of strong vasoactive drugs such as norepinephrine and phenylephrine that were used to increase blood pressure. In most receptors, bleeding 200 mL intraoperatively resulted in minimal hemodynamic fluctuations. For this study, we employed bleeding of 200 mL from the portal vein. In the second stage, with improved retrograde perfusion based on this technique, nearly 200 mL of blood and harmful metabolites generated in hepatic ischemia-reperfusion are discharged from the portal vein under stable intraoperative hemodynamic conditions [19]. By utilizing the improved retrograde perfusion technique, the release of proinflammatory cytokine-tumor necrosis factor alpha (TNF- α) and interleukin-1 (IL-1) [20, 21] is reduced. Primary mechanisms include calcium overload, the effect of leukocytes, oxygen radicals, and active factors. In the initial stage of clear blood flow after blocking, the release of a large number of oxygen radicals can lead to calcium overload in the cells and membrane phospholipids. Protein oxidation, imbalanced ion channels, and intracellular enzymes may result in more serious tissue injury after the blood flow has cleared [22]. The mechanism by which improved retrograde perfusion alleviates HIRI is the application of lowpressure perfusion to the liver using vena cava blood with reduced oxygen levels; this reduces the release of oxygen radicals and limits reperfusion injury. Additionally, with this technique, harmful metabolites that are induced by hepatic cold ischemia and retrograde perfusion rewarming are discharged as soon as possible, resulting in better protection of the donor liver. In this study, the levels of AKP, ALT, GGT, AST, and TBil in the experimental group are significantly lower than those in the control group (P<0.05) at different times after the transplantation, which demonstrates that the liver function in the experimental group recovered faster.

In conclusion, this study demonstrated that improved retrograde perfusion in SOLT can discharge harmful metabolites generated by hepatic cold ischemia and retrograde perfusion rewarming as well as limit the IRI to the graft, thus improving initial liver function and stabilizing the receptor internal environment.

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Disclosure of conflict of interest

None.

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