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ORIGINAL ARTICLE

Long-term results for living donor liver transplant recipients with hepatocellular carcinoma using intraoperative blood salvage with leukocyte depletion filter

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hepatocellular carcinoma, intraoperative blood salvage, leukocyte depletion filter, living donor liver transplantation, tumor recurrence.

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Summary

Massive intraoperative bleeding during liver transplantation often requires large amounts of blood products. The goal of this study was to investigate long-term outcomes of living donor liver transplantation (LDLT) recipients with hepatocellular carcinoma (HCC) who underwent intraoperative use of intraoperative blood salvage (IBS) and leukocyte depletion filter (LDF). In this study, we included 230 LDLT recipients with HCC from two transplantation centers, between February 2002 and December 2007. Group 1 patients (n = 121) underwent intraoperative IBS with LDF and group 2 patients (n = 109) did not. The amount of autotransfused, filtered red blood cells (RBCs) in group 1 was 1590.2 ± 1486.8 ml, which corresponded to 5.9 units of allogenic leukocyte-depleted RBCs saved. The incidences of renal dysfunction, postoperative bleeding, and urinary tract infection in group 2 were higher than in group 1 ($P < 0.05$). Recurrence-free survival rates for 1, 3, and 5 years were 91.3%, 83.3%, and 83.3%, respectively, in group 1, and 84.6%, 79.0%, and 77.4%, respectively, in group 2 ($P = 0.314$). IBS using LDF does not increase the risk of cancer recurrence during LDLT for recipients with HCC. Therefore, the use of IBS with LDF appears to be safe for LDLT recipients with HCC.

Introduction

Massive intraoperative bleeding is not an unusual finding during liver transplantation (LT) and often requires large amounts of blood products [1,2]. However, allogeneic blood transfusion during LT is associated with a wide range of complications and may delay recovery and result in overall poor outcomes [3]. The introduction of viral, bacterial, and protozoan diseases has been associated with the transfusion of blood products [4,5], which is particularly

undesirable in immunosuppressed patients. In addition, several studies have found a close link between massive intraoperative transfusion and poor survival rates after LT [6,7]. Recently, plasma-containing blood products were reported to be associated with the development of transfusion-related acute lung injury [5].

Intraoperative blood salvage (IBS) has been generally accepted as a highly effective method for reducing transfusion of red blood cells (RBCs) by saving blood products from various surgeries, including adult LT [8,9]. Autologous transfusion can substantially reduce or virtually eliminate the external source of infection. However, the safety issue surrounding the use of IBS in cancer patients has been raised because of the potential danger of systemic dissemination of cancer cells [10]. There is controversy surrounding the risk of reinfusion of the processed RBCs in these cases, but not enough data are available to confirm this risk.

Numerous studies have demonstrated that filtering the processed RBCs using a leukocyte depletion filter (LDF) can significantly decrease the number of hepatocellular carcinoma (HCC) cells in the filtered RBC aliquot [11–13]. Agreeably, in our previous *in vitro* study, we reported that LDF can significantly reduce the burden of HCC [12]. Therefore, as a continuation of our previous study to investigate the ability of LDF to remove cancer cells, we compared the tumor recurrence in living donor liver transplantation (LDLT) recipients diagnosed with HCC who used IBS with LDF with that in LDLT recipients who did not use IBS with LDF.

Materials and methods

Patients

In this study, we enrolled 182 patients older than 18 years who underwent LT as a result of HCC at Samsung Medical Center from February 2002 to December 2007. Among these patients, 61 patients were excluded because of death in the first month after transplantation without cancer recurrence ($n = 2$), deceased donor liver transplantation ($n = 20$), frequent spontaneous bacterial peritonitis in the preoperative period that prohibited the performance of IBS during transplantation ($n = 24$) or lack of need for transfusion ($n = 15$). We acquired data from 109 LT recipients with HCC during the same period from Seoul National University Hospital, in which IBS and LDF had not been used during LT. These patients were radiologically and pathologically diagnosed with HCC. These two hospitals used the same immunosuppression regimen and hepatitis B virus (HBV) prophylaxis.

The data were retrospectively collected until the 1st of January 2010. Recipients were divided into two groups depending on the use of IBS with LDF. Group 1 ($n = 121$) used IBS with LDF, whereas group 2 ($n = 109$) did not.

Intraoperative management

During LT, shed blood was suctioned from the operative field to the reservoir of Cell Saver 5 (Haemonetics, Braintree, MA, USA). Heparin (25 000 units in 1000 ml of normal saline) was used as the anticoagulant for suctioned blood. Then, the processed RBCs were filtered by LDF (Pall Biomedical Co., New York, USA) (Fig. 1). Filtered RBCs were autotransfused to the recipients in group 1 when hemoglobin was <9 g/dl. Allogenic leukocyte-depleted red blood cells (LDRBC) were transfused when autologous filtered RBCs were unavailable.

Postoperative complications

Renal dysfunction was defined as need for dialysis, and bleeding was defined as need for RBCs transfusion more than 3 units in the first week of post-transplantation. Bacterial and fungal infections were diagnosed by culture results from blood, ascites, urine, catheter, and sputum.

Immunologic regimens

Tacrolimus, steroids, and mycophenolate mofetil (MMF) were the primary agents used for immunosuppression after LT. All of the recipients were given 500 mg of methylprednisolone during the anhepatic phase and daily until postoperative day (POD) 2. The methylprednisolone was tapered to 60 mg per day for a period of 5 days. Methylprednisolone 8 mg was administered twice per day for 1 month starting on POD 8. Tacrolimus was started on POD 3. The optimal blood level of tacrolimus was adjusted to maintain a trough plasma concentration of 10–15 ng/ml during the first month, which was reduced to 5–10 ng/ml thereafter. MMF was used in combination with tacrolimus and steroids. Starting on POD 1, 750 mg MMF was administered twice a day. Cyclosporin was used in the event of tacrolimus toxicity or tacrolimus refractory rejection and was given orally twice a day. The plasma concentration of cyclosporin was adjusted

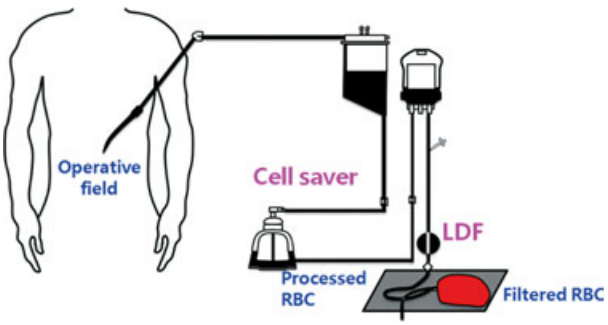

Figure 1 Schematic representation for intraoperative blood salvage with leukocyte depletion filter.

to 100–200 ng/ml. A liver biopsy was performed if acute rejection was clinically suspected. Methylprednisolone 500 mg was administered every day for 3 days if an acute rejection was confirmed by biopsy and was tapered to 60 mg per day over a period of 4 days thereafter.

Hepatitis B virus prophylaxis

All patients with HBV infection or recipients without hepatitis B surface antigen who received liver allograft with hepatitis B core antibody were given 10 000 units of hepatitis B immunoglobulin (HBIG) (Green Cross Corp., Yongin, South Korea) intravenously during the anhepatic phase, which was followed by a 7-day intravenous course of 10 000 units HBIG per day. Patients received 10 000 units intravenously every month to maintain anti-hepatitis B surface antibody titers at $\geq$200 IU/ml.

Statistics

Categorical data were compared using chi-squared or Fisher's exact tests as appropriate and continuous variables were compared using the Mann–Whitney *U*-tests. Kaplan–Meier analysis was performed for recurrence-free survival rates and both groups were compared using long-rank tests. SPSS 18.0 was used for the statistical analyses and a bilateral *P*-value of <0.05 was used to reject the null hypothesis in all cases.

Results

Preoperative characteristics of the recipients

The preoperative characteristics of recipients are summarized in Table 1. Most recipients were male and had HCC with HBV. A higher proportion of the recipients in group 1 had Child-Turchotte-Pugh grade C (57.9% in group 1 vs. 36.7% in group 2). Recipients in group 1 had lower platelet counts and serum creatinine levels than recipients in group 2 ($P = 0.033$ and $P < 0.001$, respectively). However, there was no statistically significant difference in Model for End-stage Liver Disease scores between the two groups ($P = 0.253$). In addition, there were no statistical differences in gender, age, cause of HCC, white blood cells, hemoglobin, INR, total bilirubin, and albumin between the two groups.

Table 1. The preoperative characteristics of recipients.

Variables	Group 1 (n = 121)	Group 2 (n = 109)	*p*-value
Gender			0.871
Male	97 (80.2)	86 (78.9)	
Female	24 (19.8)	23 (21.1)	
Age (year)	52.3 ± 7.1	52.6 ± 7.5	0.932
Causes of HCC			0.515
Alcohol	3 (2.1)	0 (0)	
HBV	107 (88.4)	99 (90.8)	
HCV	5 (4.1)	6 (5.5)	
HBV, HCV	2 (1.7)	1 (0.9)	
non-B, non-C	4 (3.4)	3 (2.8)	
CTP class			<0.001
A	5 (4.1)	30 (27.5)	
B	46 (38.0)	39 (35.8)	
C	70 (57.9)	40 (36.7)	
MELD	18.4 ± 8.8	16.9 ± 6.8	0.374
White blood cells (/μl)	3,024 ± 3,271	3,992 ± 1,886	0.119
Hemoglobin (g/dl)	10.7 ± 2.0	11.2 ± 2.5	0.301
Platelets (/μl)	58,660 ± 35,322	72,820 ± 70,908	0.033
INR	1.90 ± 0.93	1.79 ± 1.00	0.223
Albumin (g/dl)	2.86 ± 0.53	2.87 ± 0.65	0.892
Total bilirubin (mg/dl)	7.8 ± 11.8	4.7 ± 6.1	0.120
Creatinine (mg/dl)	0.95 ± 0.40	1.08 ± 0.42	<0.001

Values in parentheses are percentages. HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; CTP, Child-Turchotte-Pugh; MELD, Model for End-stage Liver Disease; INR, International normalized ratio.

Table 2. The intraoperative characteristics of recipients.

Variables	Group 1 (n = 121)	Group 2 (n = 109)	*P*-value
Blood loss (ml)	1427.6 ± 1225.9	1449 ± 2683.0	0.006
Transfusion (unit)			
Leukocyte-depleted RBC transfusion	3.7 ± 3.6	9.9 ± 17.9	<0.001
Fresh frozen plasma	6.8 ± 6.4	10.3 ± 19.4	0.301
Autotransfusion (ml)	1590.2 ± 1486.8	–	
Saved leukocyte-depleted RBC transfusion	5.9 ± 5.5	–	
Expected total RBC transfusion without IBS (unit)	9.6 ± 8.2	9.9 ± 17.9	0.011

LDLT, living donor liver transplantation; DDLT, deceased donor liver transplantation; RBC, red blood cells; IBS, intraoperative blood salvage.

Intraoperative characteristics of recipients

The average volume of blood loss was 1427 ml in group 1, which was less than the average of 1449 ml in group 2 ($P = 0.006$). The average number of transfused allogenic LDRBCs was 3.7 units in group 1, which was fewer than the average of 9.9 units in group 2 ($P < 0.001$). The average amounts of transfused fresh frozen plasma (FFP) in group 2 were more than the average amounts in group 1. However, there was no statistically significant difference in the average amount of transfused FFP between the two groups. The average number of autotransfused, filtered RBCs in group 1 was 1590.2 ml, which was equivalent to approximately 5.9 units of allogenic LDRBC saved

Table 3. Postoperative complications.

Variables	Group 1 (n = 121)	Group 2 (n = 109)	P-value
Renal dysfunction	2 (1.7)	9 (8.3)	0.028
Bleeding	10 (8.3)	19 (17.4)	0.046
Reoperation	12 (9.9)	18 (16.5)	0.171
Bacterial infection	70 (57.9)	81 (74.3)	0.012
Pneumonia	29 (24.0)	35 (32.1)	0.187
Urinary tract infection	15 (12.4)	55 (50.5)	<0.001
Ascites	19 (15.7)	26 (23.9	0.136
Catheter	48 (39.7)	38 (34.9	0.496
Fungus infection	6 (5.0)	2 (1.8)	0.286

Values in parentheses are percentages.

Table 4. The characteristics of hepatocellular carcinoma.

Variables	Group 1 (n = 121)	Group 2 (n = 109)	P-value
AFP (ng/ml)	509.8 ± 1662.4	453.6 ± 1849.9	0.459
Preoperative radiology			
Maximum tumor size (cm)	2.5 ± 1.5	2.7 ± 2.3	0.947
Tumor number	1.6 ± 1.0	1.8 ± 2.0	0.545
Pathology			
Maximum tumor size (cm)	2.2 ± 1.5	2.7 ± 1.5	0.019
Tumor number	2.5 ± 2.1	2.2 ± 2.0	0.365
Microvascular invasion	43 (35.5)	14 (12.8)	<0.001
Milan criteria on pathology			0.080
Within	80 (66.1)	84 (77.1)	
Beyond	41 (33.9)	25 (22.9)	

Values in parentheses are percentages. AFP, α-fetoprotein.

(Table 2). The average number of expected total RBCs transfused without IBS in group 1 was 9.6 units.

Postoperative complications

The incidences of renal dysfunction, postoperative bleeding, and urinary tract infection in group 2 were higher than in group 1 ($P < 0.05$). The incidences of reoperation, pneumonia, and ascites infection were more common in group 2 compared with group 1, but there was no statistically significant difference between the two groups (Table 3).

Characteristics of the hepatocellular carcinoma

There were no statistically significant differences in alpha-fetoprotein levels, preoperative maximum tumor size, and tumor number between group 1 and group 2 (Table 4). On pathological findings, the maximum tumor size was larger in group 2 patients than in group 1 patients ($P = 0.019$), but the incidence of microvascular invasion in group 1 was higher than that in group 2 ($P < 0.001$). There was no statistically significant difference in pathological tumor numbers between the two groups. There was also a higher proportion of group 1 patients with HCC beyond the Milan criteria than in group 2, but there was no statistically significant difference between the two groups ($P = 0.080$).

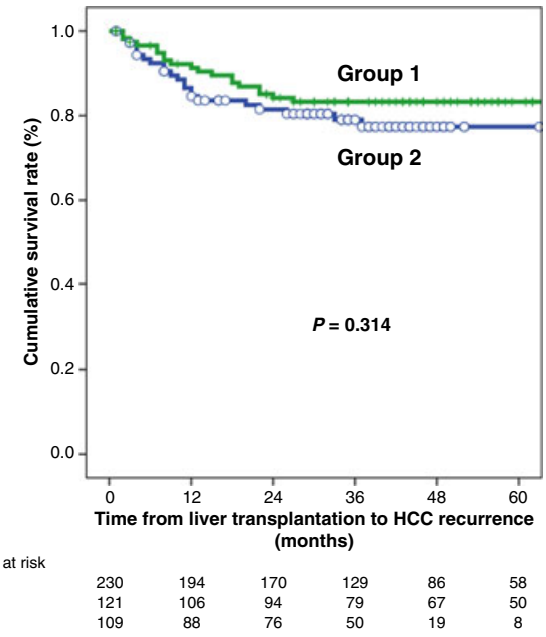

Figure 2 Recurrence-free survival rates.

Recurrence-free survival

The median follow-up was 53 months (range 8–95) in group 1 and 33 months (range 6–95) in group 2. Recurrence-free survival rates for 1, 3, and 5 years in group 1 were 91.3%, 83.3%, and 83.3%, respectively, and those in group 2 were 84.6%, 79.0%, and 77.4%, respectively. Despite the fact that the patients in group 1 had a higher incidence of microvascular invasion on pathology, the recurrence-free survival rates were not statistically different between the two groups ($P = 0.314$) (Fig. 2).

Discussion

The combined use of IBS and LDF in LDLT recipients with HCC resulted in similar long-term recurrence-free survival rates when compared with the recipients who received allogenic transfusion. Based on these results, autotransfusion of processed blood by IBS and LDF might be considered a safe method to reduce allogenic transfusion without increasing the risk of reintroducing malignant cells in LDLT recipients with HCC.

The standardization of surgical techniques and the advancement of anesthetic strategies had led to steady reduction in blood loss and transfusion needs during LDLT. However, LDLT frequently accompanies massive intraoperative bleeding, mandating prompt volume replacements. Some concerns surrounding allogenic transfusion involve possible tumor recurrence and postoperative infections [14–16], and thus, incorporation of methods to reduce the allogenic transfusion amount may render LDLT as a safe and less costly procedure.

Our study showed that postoperative complications such as renal dysfunction, postoperative bleeding, and urinary tract infection, in group 1, which used IBS and LDF, were lower than group 2. The costs of cell saver and LDF are about 240 US dollars in Korea. One unit of leukocyte-depleted RBCs is about 40 dollars. The use of IBS and LDF is more cost effective when more than 6 pints of leukocyte-depleted RBCs are necessary during transplantation. The average amount of saved leukocyte-depleted RBC transfusion when IBS and LDF were used in group 1 was about 6 pints. This study revealed that autotransfusion with IBS remarkably reduced postoperative complications and has shown to be cost effective.

One unit of LDRBC is approximately 213 ml and accounts for about 70% of hematocrits in our hospital. The hematocrits of processed blood from cell saver are about 55%, which means one unit of allogenic LDRBC is equivalent to around 271 ml of autologous RBC. Accordingly, the average volume of autotransfused RBCs in group 1 was 1590.2 ml, meaning IBS saved 5.9 units of allogenic LDRBC. If IBS had not been used in group 1, an average of 9.6 units of allogenic LDRBC would have been required during LDLT.

Despite the benefits of IBS, its use has been avoided in patients with malignancy because of the possible contamination of processed blood with malignant cells and the risk of systemic reintroduction of these cancer cells. This concern has been supported by some evidence that cancer cells pass through the IBS [10,17]. However, this issue has been a challenge because there is no clinical evidence to support this risk. In fact, in many cases, the malignant cells are already detectable in patient's circulation prior to the surgery, and many cells related to the cancer are released during tumor manipulation [18,19]. Furthermore, several studies have demonstrated evidence of both the short-term and long-term safety of autotransfusion using IBS in patients with HCC undergoing hepatectomy and they have attributed this favorable outcome to reduced the need for allogenic transfusion [20,21].

The clinically important question is whether LT recipients with HCC are likely to have a higher recurrence rate, and therefore an increased mortality rate after IBS? A prospective study involving patients undergoing LT for HCC has shown no difference in recurrence rate between those who did and did not use IBS [22]. However, it appears that an additional method to decrease or eliminate the possibility of cancer recurrence associated with IBS is necessary. In this regard, several *in vitro* studies have demonstrated the ability of LDF to completely remove malignant cells [11,23–26]. In agreement with these reports, several clinicians as well as recent guidelines from the Consensus Conference on Autologous Transfusion and National Institute for Health and Clinical Excellence have recommended the supplementation of LDF to IBS during cancer surgery [27–29]. Moreover, our previous *in vitro* study showed that LDF markedly reduced the risk for reintroduction of malignant cells [12]. A recent study also reported that IBS with LDF substantially reduced the risk of tumor cell reintroduction during the LT in recipients with nonruptured HCC tumors [13].

In our study, we present the first long-term results for a large number of LT recipients with HCC using IBS with LDF. Our study shows that recurrence-free survival rates do not differ between the two groups (Fig. 2). Filtering the processed RBCs with a LDF may significantly decrease the amount of cancer cells and thus reduce or eliminate the risk of cancer cell dissemination. Based on these results, it seems safe to use IBS with LDF during LT in recipients with HCC.

There are some limitations to our study. First, we analyzed the data of Seoul National University hospital, which had a similar number of patients, but they were not randomized. The pathologic maximum tumor size of group 2 was larger than that in group 1, but the proportion of microvascular invasion in group 1 was higher than that in group 2. Second, transfusion criteria between two centers were not same. The transfusion criteria of RBCs, FFP, and platelet concentrate in group 1 was <8 mg/dl in hemoglobin level, <3 in INR, and <30 000 of platelet counts, but that in group 2 was <25% in hematocrit, <2.5 in INR, and <20 000 of platelet counts. We thought that transfusion criteria for RBCs, FFP, and platelet concentrate were similar in two centers. Third, as this was an observational study, generalized conclusions cannot be drawn from our results. Therefore, a prospective randomized controlled trial may be required to evaluate and confirm the safety of combined IBS and LDF in LDLT recipients with HCC.

The use of IBS with LDF substantially decreased the transfusion amount of allogenic blood products and associated with lower incidence of postoperative complications, and more importantly, it does not increase the risk of cancer recurrence during LDLT for recipients with HCC. Therefore, the use of IBS with LDF appears to be safe for LDLT recipients with HCC.

Authorship

JMK: performed research, collected data, analyzed data, and wrote the paper. GSK and J-WJ: designed the study

and wrote the paper. KSS, J-BP, CHDK, SJK and S-KL: collected data and analyzed data. JSK and MSG: collected data and wrote the paper.

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