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Pre- and perioperative factors affecting infection after living donor liver transplantation

Risk factors affecting infection after liver transplantation

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Abstract

Objective: Infectious complications including sepsis that often occur after liver transplantation (LT) comprise the most frequent causes of in-hospital death. This study investigated predictors of posttransplant infectious complications to establish a strategy with which to improve short-term outcomes after LT.

Methods: We used univariate and multivariate analyses to assess pre- and perioperative risk factors for posttransplant infectious complications among 100 consecutive patients who underwent living donor LT between February 2008 and February 2010 at our institute.

Results: Multivariate analysis showed that low preoperative body cell mass (BCM) and of the absence of preoperative supplementation with branched-chain amino acids were of prognostic significance for posttransplant sepsis. In addition, Child-Pugh classification C and massive operative blood loss were independent risk factors for posttransplant bacteremia and preoperative low BCM was an independent risk factor for in-hospital death due to infection.

Conclusion: Pretransplant nutritional intervention as well as a reduction in operative blood loss would help to prevent posttransplant infectious complications developing during living donor LT. BCAA supplementation before LT affects the occurrence of infectious complications.

Keywords: liver transplantation, infection, nutrition, body cell mass, branched-chain amino acids.

Introduction

Infections after liver transplantation (LT) are the most frequent causes of morbidity and in-hospital death [1]. Patients who undergo LT are essentially regarded as being at unusually high risk for perioperative infection. For example, protein-energy malnutrition, which is common in patients with end-stage liver disease requiring LT, is considered to confer vulnerability to preoperative infection including spontaneous bacterial peritonitis and pneumonia via deteriorated immune function [2,3]. Liver transplantation itself is a massive invasion of the host. The number of intraoperatively transfused cellular blood products is also a risk factor for infections [4]. Furthermore, immunosuppression as well as multiple catheter insertion increases the risk of posttransplant infection. Consequently, infectious complications including sepsis and bacteremia often occur after LT and are the most frequent causes of in-hospital death. Therefore, the prevention of posttransplant infection plays a crucial role in improving short-term outcomes after LT.

Malnutrition is a risk factor for postoperative complications and mortality rates in patients with a cirrhotic liver who undergo surgery [5,6]. However, the impact of preoperative nutritional status as well as of nutritional intervention on postoperative infectious complications in LT remains controversial [7-10], especially in patients undergoing living donor LT (LDLT). Patients with advanced cirrhosis characteristically show a decrease

in plasma concentrations of branched-chain amino acids (BCAAs). These BCAAs serve not only as an essential substrate in the synthesis of body proteins, but also act as an important regulator of protein turnover. Moreover, BCAAs have beneficial effects on hepatic encephalopathy through the promotion of ammonia detoxification and the correction of plasma amino acid imbalance, liver regeneration, and hepatic cachexia in patients with liver diseases [11]. Improving systemic conditions, including nutritional status, to the greatest extent possible before LT facilitates early postoperative recovery. Supplementation with a BCAA-enriched nutrient mixture is reportedly beneficial not only for patients with liver cirrhosis, but also for patients undergoing hepatectomy [12-15]. However, the value of pretransplant BCAA supplementation remains unclear. The aim of the present study was therefore to examine pre- and perioperative predictors including nutritional factors such as BCAA supplementation for posttransplant infectious complications so that a strategy can be established to improve short-term outcomes after LDLT.

Methods

The present report retrospectively analyzed data from 100 consecutive adult patients (46 males and 54 females) aged ≥18 (range, 18 – 69; median, 56) years who underwent LDLT at Kyoto University Hospital between February 2008 and February 2010 after introducing the nutritional

assessment described below. The Model for End-stage Liver Disease (MELD) score was 19 (range, 7 – 46), 32 patients were ABO incompatible and 68 were identical or compatible. The indications for LT were hepatocellular carcinoma (n = 33), followed by hepatocellular diseases such as hepatitis B or C virus-associated liver cirrhosis (n = 19), progressive intrahepatic cholestatic diseases including primary biliary cirrhosis and primary sclerosing cholangitis (n = 13), fulminant hepatic failure (n = 11) and other causes (n = 24). The patients provided written informed consent before the start of the study, which was approved by the Ethics Committee of Kyoto University and conducted in accordance with the Declaration of Helsinki of 1975 as revised in 1996.

We introduced body composition analysis using multifrequency bioelectrical impedance with eight tactile electrodes (InBody 720; Biospace, Tokyo, Japan) in February 2008 for patients undergoing LT. Patients fast for at least 3 hours and void immediately before starting the analysis. Various parameters are automatically measured, including body mass index, intra- and extracellular water, body fat mass, protein, and body cell mass (BCM), which is the sum of intracellular fluid and protein and a reliable parameter of nutritional status. The BCM is automatically calculated by the InBody 720 for each patient and displayed as a normal range (e.g. 23.0 ~ 28.1 kg). Low and high BCM values are below the lower limit and above the upper limit, respectively. Ten patients who could not undergo

preoperative InBody 720 examination due to undergoing emergency surgery were excluded from the BCM analysis.

Preoperative nutritional therapy was administered for about 2 weeks before LDLT at the discretion of the surgeon or attending physician after admission to our department. The therapy consisted of a nutrient mixture enriched with branched-chain amino acids (BCAA; Aminoleban EN; Otsuka Pharmaceutical Co., Tokyo, Japan), BCAA nutrients (Livact; Ajinomoto Pharma Co., Tokyo, Japan) or none. Thirty-seven of the patients received the preoperative BCAA-enriched nutrient mixture (100 g/day), 28 received BCAA nutrients (12.45 g/day), and 35 received no nutritional therapy. Dieticians adjusted the type and amount of food for each patient to maintain a total caloric intake of 35 - 40 kcal/kg and a protein intake of 1.2 to 1.5 g/kg including BCAA nutrients according to the guidelines of the European Society of Parenteral and Enteral Nutrition.

The selection criteria for the recipients as well as surgical techniques for recipient operations have been described in detail elsewhere [16-18]. Immunosuppressive therapy usually consisted of tacrolimus or cyclosporine and low-dose steroids as described elsewhere [18,19].

We examined preoperative risk factors (including preoperative nutritional parameters) for posttransplant sepsis, posttransplant bacteremia and in-hospital death due to infection. Data regarding the following recipient variables for each patient were analyzed: age of recipient, gender,

original disease underlying the need for LT, ABO compatibility, Child-Pugh classification, MELD score, graft type (right or left lobe), graft-recipient weight ratio (GRWR), operative duration, operative blood loss, pretransplant BCM, and preoperative nutritional therapy. We defined conditions fulfilling the diagnostic criteria for systemic inflammatory response syndrome with infections including blood, urine and pulmonary infection as sepsis [20]. Infections were defined using the criteria proposed by the Centers for Disease Control and based on reports regarding liver transplant patients [21]. Isolation of bacteria other than common skin contaminants from a single blood culture in the presence of clinical symptoms or of infection was considered bacteremia. When caused by common skin contaminants, bacteremia was considered significant only if an organism was isolated from two blood cultures and clinical signs of infection were evident.

Statistical analysis

Categorical variables were compared using the χ^2 test or Fisher's exact test where appropriate. Any variable identified as significant ($P < 0.05$) or with $P < 0.10$ in univariate analyses using the above tests was considered a candidate for multivariate analysis using multiple logistic regression models. A *P* value of < 0.05 was considered significant. All data were statistically analyzed using JMP 5.0.1 software.

Results

Posttransplant sepsis

Univariate analysis showed that age <60 years, MELD score ≥20, low pretransplant BCM and the absence of preoperative supplementation with the BCAA-enriched nutrient mixture were of prognostic significance for posttransplant sepsis (Table 1). Multivariate analysis revealed that low pretransplant BCM ($p = 0.032$) and no preoperative BCAA-enriched nutrient supplementation ($p = 0.020$) were of independent prognostic significance for posttransplant sepsis (Table 2).

Bacteremia

Age <60 years, Child-Pugh classification C, perioperative blood loss ≥10 L and no preoperative BCAA-enriched supplementation were risk factors for bacteremia (Table 3). Multivariate analysis revealed that Child-Pugh classification C ($p = 0.002$) and perioperative blood loss ≥10 L ($p = 0.018$) were independent risk factors for posttransplant bacteremia (Table 4).

In-hospital death due to infection

Age <60 years, Child-Pugh classification C and low preoperative BCM were significant risk factors for in-hospital death due to infection (Table 5).

Multivariate analysis showed that only low preoperative BCM ($p = 0.004$) was an independent risk factor (Table 6).

Discussion

The present study examined risk factors affecting three types of infectious complications after LDLT. We identified the independent risk factors as Child-Pugh classification C, massive perioperative blood loss, low pretransplant BCM and the absence of preoperative supplementation with a BCAA-enriched nutrient mixture. Decompensated liver cirrhosis indicated by Child-Pugh classification C is usually accompanied by deteriorated immune function and nutritional status at the time of LT. Child-Pugh classification C was thus undoubtedly a risk factor of postoperative infection, which is in line with the results of our recent report [22]. Massive perioperative bleeding is an established factor for postoperative complications of digestive surgery as well as LT and massive blood loss is usually associated with massive blood transfusion. Homologous blood transfusion has adverse effects such as a risk of infection and graft-versus-host disease. This detrimental effect is supposed to be caused by nonspecific immunosuppression such as decreased CD4/CD8 ratios [23,24] and natural killer cell activity [25,26]. We recently reported that low pretransplant BCM and the absence of preoperative BCAA-enriched supplementation are closely associated with postoperative sepsis [27]. The

present findings supported not only our previous results but also demonstrated the powerful impact of pretransplant nutritional conditions and preoperative treatment with BCAA-enriched nutrient mixture on infectious complications.

The reason for the beneficial effects of pretransplant BCAA supplementation, however, remains unclear. One possible explanation is improvement in pretransplant nutritional status. Some nutritional parameters, such as prealbumin, total lymphocyte count, and BCAA/tyrosine ratio, were significantly improved by pretransplant nutritional intervention including BCAA-enriched nutrient mixture (in submission). Another possible reason is the improvement of the immune system. Bassit et al. reported that BCAA supplementation improves the ability of peripheral blood mononuclear cells to proliferate in response to mitogens after long distance intense exercise [28]. Lorenzo et al. reported that septic patients receiving a high-BCAA preparation showed decreased mortality and improved nutritional parameters [29]. In patients with advanced liver cirrhosis, Kakazu et al. showed that elevating extracellular concentration of BCAAs ex vivo improved the function of myeloid dendritic cells [30]. Our results suggest that preoperative BCAA-enriched supplementation can help to prevent postoperative sepsis through nutritional and immune improvement, although a randomized controlled study is required to confirm this hypothesis. Taken together with our

findings demonstrating that the absence of posttransplant enteral nutrition is a risk factor affecting in-hospital mortality after LT [1], perioperative nutritional treatment represents a promising strategy for improving short-term outcomes after LT.

Based on the current findings, we considered establishing an interventional strategy against these risk factors to prevent posttransplant infectious complications. Child-Pugh classification C itself is an indication for LT. In contrast, massive blood loss, pretransplant low BCM and the absence of preoperative BCAA-enriched supplementation are factors that can be altered to some extent. Blood loss can be reduced by more careful surgical maneuvering and the frequent application of hemostatic devices during dissection of the liver from surrounding ligaments and the inferior vena cava. The sum of intracellular fluid and body protein, BCM, is considered a highly reliable parameter of nutritional status. Especially for patients undergoing LT who usually have abundant extracellular fluid such as edema and ascites, BCM can assess their nutritional status more accurately than other nutritional parameters including body mass index and lean body mass. Low BCM in patients with cirrhosis suggests a decrease in skeletal muscle volume, which could interfere with early postoperative mobilization and result in pulmonary complications including aspiration pneumonia and atelectasis. Therefore, we have recently introduced a pretransplant rehabilitation program to encourage early postoperative

mobilization and avert pulmonary dysfunction. Since LDLT is an elective procedure that differs from deceased donor LT, a pretransplant rehabilitation program can be implemented until the day of transplant.

The prevalence of metabolic disorders including metabolic syndrome on liver–transplant population has recently attracted attention [31-33]. The prevalence of metabolic syndrome in post-LT patients is significantly higher than that estimated in the general population and metabolic syndrome is associated with an increased risk of major vascular events and long-term fibrosis progression. Therefore, prevention of post-LT metabolic syndrome would also be a crucial objective of perioperative nutritional treatment.

Supplementation with a BCAA-enriched nutrient mixture is reportedly beneficial not only for patients with liver cirrhosis but also for patients undergoing hepatectomy [23-26]. However, the value of pretransplant BCAA supplementation has remained unclear. Our results suggest that preoperative BCAA-enriched supplementation can help to prevent postoperative sepsis, although a randomized controlled study is required to confirm this notion. Taken together with our findings demonstrating that the absence of posttransplant enteral nutrition is a risk factor affecting in-hospital mortality after LT [1], perioperative nutritional treatment should be a promising strategy to improve short-term outcomes after LT.

Conclusion

Preoperative nutritional status, supplementation with a nutrient mixture enriched with BCAAs and massive operative blood loss were closely associated with the occurrence of posttransplant infectious complications. Perioperative management including nutritional therapy is needed to improve short-term outcomes after LT.

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Table 1. Univariate analysis of factors affecting posttransplant sepsis.

Table 2. Multivariate analysis of factors affecting posttransplant sepsis.

Table 3. Univariate analysis of factors affecting posttransplant bacteremia.

Table 4. Multivariate analysis of factors affecting posttransplant bacteremia.

Table 5. Univariate analysis of factors affecting in-hospital death due to infection.

Table 6. Multivariate analysis of factors affecting in-hospital death due to infection.

Table(s)
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Table 1. Univariate analysis of factors affecting posttransplant sepsis

Variable		Incidence of event	*P* value
Age (y)	<60 (n=68)	72%	0.001
	≥60 (n=32)	38%	
Gender	Male (n=46)	52%	0.051
	Female (n=54)	70%	
Original disease	HCC (n=34)	50%	0.460
	HBV/HCV (n=19)	68%	
	PBC/PSC (n=20)	70%	
	FHF (n=8)	75%	
	Others (n=19)	58%	
ABO blood type	Compatible (n=61)	57%	0.166
	Incompatible (n=39)	71%	
Child-Pugh	A, B (n=39)	51%	0.112
	C (n=61)	67%	
MELD score	<20 (n=55)	51%	0.021
	≥20 (n=45)	73%	
GRWR	<0.8% (n=28)	50%	0.163
	≥0.8% (n=72)	65%	

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Graft	Rt (n=57)	61%	0.924
	Lt (n=43)	60%	
Operative time	<12h (n=25)	68%	0.403
	≥12h (n=75)	59%	
Operative blood loss	<10L (n=65)	58%	0.476
	≥10L (n=35)	66%	
Preoperative BCM	Low (n=24)	83%	0.002
	Normal or high (n=64)	48%	
Preoperative BCAA enriched nutrient mixture			0.001
	With (n=37)	38%	
	Absent (n=63)	73%	

HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; PBC, primary biliary cirrhosis; PSC, primary sclerosing cirrhosis; FHF, fulminant hepatic failure; MELD, model for end-stage liver disease; GRWR, graft to recipient weight ratio; BCM, body cell mass; BCAA, branched-chain amino acids.

Table 2. Multivariate analysis of factors affecting posttransplant sepsis

Variable	Odds ratio	95% CI	*P*
Preoperative low BCM	4.633	1.493-17.701	0.032
Absence of preoperative BCAA enriched nutrient mixture	3.201	1.202-7.849	0.020

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Table 3. Univariate analysis of factors affecting posttransplant bacteremia

Variable		Incidence of event	*P* value
Age (y)	<60 (n=68)	51%	0.011
	≥60 (n=32)	25%	
Gender	Male (n=46)	39%	0.470
	Female (n=54)	46%	
Original disease	HCC (n=34)	41%	0.880
	HBV/HCV (n=19)	53%	
	PBC/PSC (n=20)	45%	
	FHF (n=8)	38%	
	Others (n=19)	37%	
ABO blood type	Compatible (n=61)	39%	0.245
	Incompatible (n=39)	52%	
Child-Pugh	A, B (n=39)	23%	0.001
	C (n=61)	56%	
MELD score	<20 (n=55)	35%	0.059
	≥20 (n=45)	53%	
GRWR	<0.8% (n=28)	39%	0.639
	≥0.8% (n=72)	44%	

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Graft	Rt (n=57)	47%	0.309
	Lt (n=43)	33%	
Operative time	<12h (n=25)	40%	0.726
	≥12h (n=75)	44%	
Operative blood loss	<10L (n=65)	34%	0.012
	≥10L (n=35)	60%	
Preoperative BCM	Low (n=24)	54%	0.093
	Normal or high (n=64)	34%	
Preoperative BCAA enriched nutrient mixture			0.015
	With (n=37)	26%	
	Absent (n=63)	52%	

HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; PBC, primary biliary cirrhosis; PSC, primary sclerosing cirrhosis; FHF, fulminant hepatic failure; MELD, model for end-stage liver disease; GRWR, graft to recipient weight ratio; BCM, body cell mass; BCAA, branched-chain amino acids.

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Table 4. Multivariate analysis of factors affecting posttransplant bacteremia

Variable	Odds ratio	95% CI	*P*
Child-Pugh C	4.253	1.731-11.294	0.001
Operative blood loss ≥10L	2.983	1.229-7.541	0.018

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Table 5. Univariate analysis of factors affecting in-hospital death due to infection

Variable		Incidence of event	*P* value
Age (y)	<60 (n=68)	19%	0.017
	≥60 (n=32)	3%	
Gender	Male (n=46)	17%	0.369
	Female (n=54)	11%	
Original disease	HCC (n=34)	6%	0.462
	HBV/HCV (n=19)	21%	
	PBC/PSC (n=20)	20%	
	FHF (n=8)	13%	
	Others (n=19)	16%	
ABO blood type	Compatible (n=61)	13%	0.684
	Incompatible (n=39)	16%	
Child-Pugh	A, B (n=39)	5%	0.030
	C (n=61)	20%	
MELD score	<20 (n=55)	9%	0.118
	≥20 (n=45)	20%	
GRWR	<0.8% (n=28)	7%	0.192
	≥0.8% (n=72)	17%	

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Graft	Rt (n=57)	16%	0.550
	Lt (n=43)	12%	
Operative time	<12h (n=25)	8%	0.293
	≥12h (n=75)	16%	
Operative blood loss	<10L (n=65)	11%	0.213
	≥10L (n=35)	20%	
Preoperative BCM	Low (n=24)	29%	0.003
	Normal or high (n=64)	5%	
Preoperative BCAA enriched nutrient mixture			0.884
	With (n=37)	14%	
	Absent (n=63)	15%	

HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; PBC, primary biliary cirrhosis; PSC, primary sclerosing cirrhosis; FHF, fulminant hepatic failure; MELD, model for end-stage liver disease; GRWR, graft to recipient weight ratio; BCM, body cell mass; BCAA, branched-chain amino acids.

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Table 6. Multivariate analysis of factors affecting in-hospital death due to infection

Variable	Odds ratio	95% CI	*P*
Preoperative low BCM	8.372	2.092-42.181	0.004