Assessment of blood-products use as predictor of pulmonary complications and surgical-site infection after hepatectomy for hepatocellular carcinoma

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Abstract

Background In perioperative management after hepatectomy, some patients require fresh frozen plasma (FFP) to treat coagulopathy associated with blood loss. However, several studies have suggested a correlation between blood products and pulmonary complications or surgical-site infection (SSI).

Methods The subjects were 99 patients who underwent hepatectomy for hepatocellular carcinoma without plasma exchange for postoperative liver failure in the Department of Surgery, Jikei University Hospital, between January 2000 and December 2006. We investigated the association of 16 factors including age; gender; preoperative ICG_{R15}; type of resection; concomitant resection of other digestive organs; duration of operation; blood loss; hepatitis virus status; postoperative minimum platelet count, maximum serum total bilirubin (max T-Bil), minimum serum albumin, or minimum prothrombin time; and the dose of red-blood-cell concentration (RC), FFP, platelet concentration, or albumin given in relation to postoperative pulmonary complications and SSI.

Results In univariate analysis, pulmonary complications were correlated with gender ($P = 0.012$), max T-Bil ($P = 0.043$), dose of RC given ($P = 0.007$), dose of FFP given ($P < 0.001$), and dose of albumin given ($P < 0.001$). In multivariate analysis, pulmonary complications were correlated with FFP given ($P = 0.031$) and albumin given

($P = 0.020$), while the incidence of SSI was not correlated with any factors.

Conclusion Excessive FFP and albumin administration may cause pulmonary complications after hepatectomy.

Keywords Fresh frozen plasma · Hepatectomy · Hepatocellular carcinoma · Pulmonary complication · Surgical-site infection

Introduction

In Japan, blood products such as fresh frozen plasma (FFP) and albumin have been administered rather liberally after hepatectomy for hepatocellular carcinoma (HCC) to maintain plasma osmotic pressure and coagulation factor levels [1, 2] because appropriate guidelines for blood-products transfusion had not yet been established [3–6]. Then, in 1999, the guidelines for administration of blood preparations were released from the Japanese Ministry of Health and Welfare [7]. Indications of FFP use have been limited to reduce consumption of FFP.

Several studies have suggested the involvement of FFP in pulmonary complications and surgical-site infections (SSI) after surgery [8, 9]. In recent years, the use of FFP has partially been replaced by albumin preparations. However, there are no standardized guidelines for the use of albumin preparations [10–13]. On the other hand, in perioperative management of hepatectomy for HCC, coagulopathy and albumin composition dysfunction by concomitant chronic liver disease are not unusual, and administration of blood components may be essential. Therefore, the usefulness and risk of blood-products use in perioperative management of hepatectomy for HCC needs to be evaluated. In this study, we retrospectively

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investigated factors pertinent to pulmonary complications and SSI after hepatectomy for HCC to clarify risk factors for such complications, with special reference to perioperative blood-products use.

Methods

Between January 2000 and December 2006, 101 patients underwent hepatectomy for HCC in the Department of Surgery, Jikei University Hospital. Of these, two patients who required plasma exchange for postoperative liver failure were excluded, and the remaining 99 patients were studied. Generally, the extent of hepatectomy was determined based on ICG_{R15} before surgery and hepatic reserve, as described by Makuuchi et al. [14]. The use of blood products was determined by attending surgeons, and the dose of blood products given was judged based on intraoperative blood loss, and postoperative hemoglobin level, platelet count, serum albumin level, and prothrombin time (PT).

We investigated the association of pulmonary complications and SSI with the following 16 factors: age; gender; preoperative ICG_{R15}; type of resection; concomitant resection of other digestive organs; duration of operation; blood loss; hepatitis virus status; postoperative data of minimum platelet count (min Plt), maximum serum total bilirubin (max T-Bil), minimum serum albumin (min Alb), or minimum prothrombin time (min PT); and the dose of red-blood-cell concentration (RC), FFP, platelet concentration (PC), or albumin given. Pulmonary complications were defined as postoperative pneumonia; postoperative respiratory failure with pyrexia, dyspnea, and a pulmonary infiltrate on chest X-rays; or pleural effusion that required thoracentesis. SSI was defined as surgical wound infection with purulent discharge and bacterial isolation, or abdominal abscess with pyrexia. The type of resection was classified into two types:

Table 1 Types of resection

Type of resection	Number
Anatomical hepatic resection	
Extended right lobectomy	3
Extended left lobectomy	2
Right lobectomy	12
Left lobectomy	2
Posterior segmentectomy	3
Lateral segmentectomy	5
Subsegmentectomy	6
Caudate lobectomy	2
Limited partial resection	64

anatomical hepatectomy (extended lobectomy, lobectomy, segmentectomy, or subsegmentectomy) and limited partial resection.

Statistical analysis

The data are expressed as mean $\pm$ SD. Univariate analysis was performed using non-paired Student's *t* test and χ^2 test.

Table 2 Postoperative complications after hepatectomy

Complications	Number
SSI	
Surgical wound infection	12
Intraperitoneal abscess	1
Pulmonary complication	
Postoperative pneumonia	9
Respiratory failure	3
Pleural effusion	1
Others	
Bile leakage	6
Hepatic failure	1
Small-bowel obstruction	2
Intractable ascites	1
Upper gastrointestinal hemorrhage	1

SSI Surgical site infection

Table 3 Patient characteristics

Variable	Data
Age (years)	61.2 $\pm$ 11.1
Gender (male:female)	84:15
ICG _{R15} (%)	14.2 $\pm$ 9.4
Type of resection (anatomical:partial)	35:64
Resection of digestive organs (yes:no)	6:93
Duration of operation (min)	287.7 $\pm$ 120.3
Blood loss (g)	1,097.4 $\pm$ 1,222.5
Hepatitis virus (HBV:HCV:no)	39:43:17
Max T-Bil (mg/dl)	1.8 $\pm$ 1.0
Min PT (%)	69.7 $\pm$ 12.9
Min Plt ($\times 10^3/\mu\text{l}$)	115.8 $\pm$ 46.0
Min Alb (g/dl)	3.0 $\pm$ 0.4
RC given (units)	1.9 $\pm$ 3.9
FFP given (units)	8.2 $\pm$ 14.5
PC given (units)	1.5 $\pm$ 5.8
Albumin given (g)	49.9 $\pm$ 99.3

HBV Hepatitis B virus, HCV hepatitis C virus, max T-Bil maximum serum postoperative total bilirubin, min PT minimum postoperative prothrombin time, min Plt minimum postoperative platelet, min Alb minimum postoperative serum albumin, RC red-blood-cell concentration, FFP fresh frozen plasma, PC platelet concentration

Data are mean $\pm$ SD unless otherwise stated

Table 4 Univariate analysis of clinical variables and SSI after hepatectomy

Factor	SSI		<i>P</i> value (univariate)
	Yes (<i>n</i> = 13)	No (<i>n</i> = 86)	
Age (years)	59.5 ± 8.0	61.4 ± 11.4	0.553
Gender (male:female)	13:0	71:15	0.102
ICG _{R15} (%)	14.3 ± 6.0	14.1 ± 9.8	0.971
Type of resection (anatomical:partial)	5:8	30:56	0.801
Resection of digestive organs (yes:no)	1:12	5:81	0.791
Duration of operation (min)	325.8 ± 116.0	282.0 ± 120.6	0.223
Blood loss (g)	1,188.8 ± 1,171.9	1,083.6 ± 1,236.0	0.774
Hepatitis virus (HBV:HCV:no)	4:6:3	35:37:14	0.736
Max T-Bil (mg/dl)	2.2 ± 1.3	1.7 ± 1.0	0.109
Min PT (%)	69.5 ± 15.5	69.8 ± 12.5	0.951
Min Plt (×10 ³ /μl)	110.1 ± 45.4	116.6 ± 46.3	0.634
Min Alb (g/dl)	2.9 ± 0.4	3.1 ± 0.4	0.230
RC given (units)	2.0 ± 3.8	1.9 ± 3.9	0.937
FFP given (units)	15.2 ± 23.2	7.1 ± 12.6	0.063
PC given (units)	1.5 ± 5.5	1.5 ± 5.9	0.961
Albumin given (g)	78.8 ± 200.2	45.5 ± 74.5	0.261

SSI Surgical site infection, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *max T-Bil* maximum postoperative serum total bilirubin, *min PT* minimum postoperative prothrombin time, *min Plt* minimum postoperative platelet, *min Alb* minimum postoperative serum albumin, *RC* red-blood-cell concentration, *FFP* fresh frozen plasma, *PC* platelet concentration

Table 5 Univariate analysis of clinical variables and postoperative pulmonary complications after hepatectomy

Factor	Pulmonary complications		<i>P</i> value (univariate)
	Yes (<i>n</i> = 13)	No (<i>n</i> = 86)	
Age (years)	64.5 ± 8.3	60.6 ± 11.3	0.245
Gender (male:female)	8:5	76:10	0.012
ICG _{R15} (%)	13.8 ± 7.2	14.2 ± 9.7	0.874
Type of resection (anatomical:partial)	6:7	29:57	0.382
Resection of digestive organs (yes:no)	0:13	6:80	0.326
Duration of operation (min)	331.2 ± 132.9	281.2 ± 117.8	0.164
Blood loss (g)	1,647.6 ± 1,858.2	1,014.2 ± 1,087.3	0.082
Hepatitis virus (HBV:HCV:no)	6:5:2	33:38:15	0.867
Max T-Bil (mg/dl)	2.3 ± 1.6	1.7 ± 0.9	0.043
Min PT (%)	63.4 ± 13.5	70.7 ± 12.6	0.068
Min Plt (×10 ³ /μl)	113.3 ± 71.3	116.1 ± 41.9	0.840
Min Alb (g/dl)	3.0 ± 0.5	3.0 ± 0.4	0.682
RC given (units)	4.6 ± 6.6	1.5 ± 3.2	0.007
FFP given (units)	26.8 ± 25.2	5.3 ± 9.6	<0.001
PC given (units)	3.1 ± 7.5	1.2 ± 5.5	0.286
Albumin given (g)	179.8 ± 211.7	30.2 ± 45.4	<0.001

HBV Hepatitis B virus, *HCV* hepatitis C virus, *max T-Bil* maximum postoperative serum total bilirubin, *min PT* minimum postoperative prothrombin time, *min Plt* minimum postoperative platelet, *min Alb* minimum postoperative serum albumin, *RC* red-blood-cell concentration, *FFP* fresh frozen plasma, *PC* platelet concentration

Multivariate analysis was performed using logistic-regression analysis. A *P* value <0.05 was regarded as significant.

Results

Type of resection, postoperative complications, and patient characteristics

Types of resection are listed in Table 1 and postoperative complications in Table 2. Postoperative complications

developed in 33 of the 99 patients (33.3%), including pulmonary complications in 13, SSI in 13, and hospital death due to respiratory failure in 1 patient (1.1%). Patient characteristics are listed in Table 3.

Association between clinical variables and postoperative SSI

Table 4 lists the relationship between clinical variables and SSI after hepatectomy for HCC. In univariate analysis, the incidence of SSI did not correlate with any factors.

Association between clinical variables and postoperative pulmonary complications

Table 5 lists the relationship between clinical variables and pulmonary complications after hepatectomy for HCC. In univariate analysis, pulmonary complication was more common in females ($P = 0.012$) and associated with higher max T-Bil ($P = 0.043$), and dose of RC given ($P = 0.007$), FFP given ($P < 0.001$) and albumin given ($P < 0.001$). In multivariate analysis, dose of FFP given ($P = 0.031$) and albumin given ($P = 0.020$) were associated with pulmonary complications (Table 6), which suggests that excessive FFP or albumin use may cause pulmonary complications. Table 7 lists the clinical parameters of 13 patients with postoperative pulmonary complications.

Table 6 Multivariate analysis of clinical variables and postoperative pulmonary complications after hepatectomy

Factor	Odds ratio (95% CI)	<i>P</i> value (multivariate)
Gender (female)	4.986 (0.889–27.956)	0.068
Max T-Bil (mg/dl)	0.405 (0.122–1.345)	0.140
RC given (units)	0.968 (0.760–1.232)	0.791
FFP given (units)	1.089 (1.008–1.177)	0.031
Albumin given (g)	1.015 (1.002–1.027)	0.020

Max T-Bil Maximum postoperative serum total bilirubin, *FFP* fresh frozen plasma

Discussion

In 1985, the Hospital Transfusion Committee in the United States recommended criteria for blood-products administration [15]. In Europe and in the United States, blood-products administration has been minimized for many years [16–19]. In Japan, on the other hand, the use of FFP transfusion has been rather liberal to maintain the circulating plasma volume and supplement the coagulation factors. In Japan, the guidelines for administration of blood preparations were established by the Ministry of Health and Welfare in 1999 [7]. FFP transfusion is limited to supplementing coagulation factors, while albumin preparation is recommended to supplement plasma protein. This practice did reduce the usage of FFP. Japanese guidelines for administration of blood preparations advocate that FFP should be indicated for patients with a PT value of 30% or less and an activated partial thromboplastin time value 1.5 times higher than the reference value established at each hospital. In addition, FFP should be indicated when the volume of blood loss during surgery corresponds to 100% or more of the circulating blood volume. To maintain the circulating plasma volume, isotonic albumin preparations should be administered. For protein source supplementation, intravenous hyperalimentation or enteral nutrition is indicated. Various plasma fraction preparations have been developed and administered, which contribute to sparing the use of FFP.

Excessive intraoperative blood loss and blood transfusion affect postoperative complications and prognoses [2, 20, 21], and recent studies have reported a relationship

Table 7 Clinical variables of patients with postoperative pulmonary complications

Age (years)	Gender	ICG _{R15} (%)	Type of resection	Resection of digestive organs	Duration of operation (min)	Blood loss (g)	Hepatitis virus	Max T-Bil (mg/dl)	Min PT (%)	Min Plt ($\times 10^3/\mu$ l)	Min Alb (g/dl)	RC given (units)	FFP given (units)	PC given (units)	Albumin given (g)
64	M	16	Anatomical	No	290	1,104	HCV	2.1	58	42	2.7	0	40	20	12.5
57	M	8	Anatomical	No	400	2,650	HBV	1.1	63	292	3.2	4	21	0	62.5
57	M	13	Partial	No	195	225	HBV	1.1	82	122	3.4	0	0	0	0
74	F	18	Anatomical	No	330	4,500	HCV	6.6	58	85	3.4	20	64	0	212.5
67	F	34	Partial	No	135	475	HCV	2.8	37	70	2.5	4	48	0	275
66	M	8	Anatomical	No	330	610	No	3.2	66	122	2.5	4	24	0	362.5
76	M	15	Anatomical	No	300	1,300	HBV	2.3	64	113	3.0	2	12	0	50
76	F	7	Partial	No	490	4,235	No	2.5	57	92	3.4	12	24	20	200
71	M	12	Anatomical	No	585	5,230	HCV	2.1	72	54	4.1	14	40	0	325
66	F	15	Partial	No	410	250	HCV	1.3	66	73	2.6	0	0	0	100
58	M	16	Partial	No	210	10	HBV	0.9	87	210	3.2	0	0	0	0
53	M	10	Partial	No	450	730	HBV	3.5	49	80	2.8	0	75	0	737.5
53	F	7	Partial	No	180	100	HBV	1	66	117	2.6	0	0	0	0

HBV Hepatitis B virus, *HCV* hepatitis C virus, *max T-Bil* maximum postoperative serum total bilirubin, *min PT* minimum postoperative prothrombin time, *min Plt* minimum postoperative platelet, *min Alb* minimum postoperative serum albumin, *RC* red-blood-cell concentration, *FFP* fresh frozen plasma, *PC* platelet concentration

between allogenic blood transfusion and immunomodulatory effects [22–26]. Concerning the mechanism for immunosuppressive effects of blood transfusion, soluble HLA class I molecules and soluble Fas-ligands released by leukocytes in blood-transfusion preparations inhibit the activity of NK cells and cytotoxic T cells, which reduce immune capacity, inducing postoperative infectious diseases such as postoperative pneumonia and wound infection [8, 26–31]. Since blood preparations are derived from donations, massive administration of blood preparations should be avoided.

Nevertheless, in perioperative management of hepatectomy for HCC, it is sometimes necessary to supplement blood components following extensive blood loss and hepatic dysfunction. Administration of blood products including FFP and albumin preparation at an optimal dose may be important to prevent postoperative complications. Changes in the condition during or after hepatectomy differ among patients with hepatopathy such as liver cirrhosis; such patients often require blood products including FFP and albumin preparation therapy. Criteria should be established for the use of blood products in hepatic surgery for cirrhotic patients and in perioperative management, so that complications of hepatic resection can be minimized. Based on these guidelines, conditions requiring transfusion during hepatectomy or in perioperative management and side effects of blood products use should be reviewed, and criteria for administering blood products must be established.

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