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BRIEF ARTICLE

Advantage of autologous blood transfusion in surgery for hepatocellular carcinoma

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Abstract

AIM: To evaluate the significance of autologous blood transfusion (AT) in reducing homologous blood transfusion (HT) in surgery for hepatocellular carcinoma (HCC).

METHODS: The proportion of patients who received HT was compared between two groups determined by the time of AT introduction; period A (1991-1994, n = 93) and period B (1995-2000, n = 201). Multivariate logistic regression analysis was performed in order to identify independent significant predictors of the need for HT. We also investigated the impact of AT and HT on long-term postoperative outcome after curative surgery for HCC.

RESULTS: The proportion of patients with HT was significantly lower in period B than period A (18.9% *vs* 60.2%, $P < 0.0001$). Multivariate logistic regression analysis identified AT administration as a significant independent predictor of the need for HT ($P < 0.0001$). Disease-free survival in patients with AT was comparable to that without any transfusion. Multivariate analysis identified HT administration as an independent significant factor for poorer disease-free survival ($P = 0.0380$).

CONCLUSION: AT administration significantly decreased the need for HT. Considering the postoperative survival disadvantage of HT, AT administration could improve the long-term outcome of HCC patients.

Key words: Hepatocellular carcinoma; Surgery; Autologous blood transfusion; Homologous blood transfusion

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INTRODUCTION

Surgical resection is a safe and effective treatment for hepatocellular carcinoma (HCC). Because HCC usually develops in patients with liver cirrhosis, most of such patients present with bleeding tendencies related to

chronic liver dysfunction[1-3]. Therefore, surgery for HCC frequently requires intraoperative transfusion. Homologous blood transfusion (HT) is necessary for patients with excessive intraoperative bleeding, though this is still associated with risks of infections and/or immunological complications[4,5]. Moreover, evidence suggests that HT may be adversely associated with tumor recurrence and poor postoperative survival in various kinds of cancers[6-13]. Autologous transfusion (AT), which represents collection and reinfusion of the patient's own blood or blood components before surgery, and has been developed as a strategy to reduce the need for HT, is currently used for patients scheduled for surgery for various diseases including HCC[11,14-17]. It has been the policy in our hospital since 1995 to prepare for AT for patients scheduled for HCC surgery. To date, several investigators have examined the significance of AT in terms of reducing the need for HT and of postoperative outcome, but only a few were conducted with proper statistical analyses to identify the significance of AT[16,17].

In the present study, we reviewed the frequency of HT and AT administration in patients undergoing surgery for HCC, and statistically analyzed the significant factors that could predict the need for HT. We also compared the difference between the effects of AT and HT on long-term postoperative outcome after curative surgery for HCC.

MATERIALS AND METHODS

The present study included 294 patients with HCC who underwent hepatic resection at the Department of Surgery, Osaka University Hospital between January 1991 and December 2000. In 93 patients between 1991 and 1994 (period A), AT was not administered, and, when blood was needed, HT was administered. Between 1995 and 2000 (period B), AT was carried out preoperatively in the remaining 201 patients provided: (1) they agreed to the storage; (2) their hemoglobin (Hb) level was $\geqslant$ 11.0 g/dL before storage; and (3) they were free of severe cardiopulmonary and/or cerebrovascular diseases, or infection. Autologous blood was collected 1 to 3 times, with 200-400 mL of blood at a time. The blood was stored in a liquid state without freezing. Iron supplements were given daily to the patients who deposited the autologous blood in the post-storage period. In addition, if the total volume of the collected blood was $\geqslant$ 800 mL, recombinant human erythropoietin was administered. All through the study period, during hepatic resection, blood transfusion was carried out when the Hb level fell to < 8.0 g/dL in patients with normal cardiopulmonary function or < 9.0 g/dL in patients with severe cardiopulmonary or cerebrovascular diseases. In patients who had previously deposited autologous blood, autologous blood was first used prior to homologous blood. In this study, patients who required HT were defined as the HT group, irrespective of prior AT, and the remaining patients without HT were defined as the non-HT group. Furthermore, patients in whom only AT was performed were defined as the AT group, and patients without AT or HT were as defined as the non-transfusion group.

Hospital records were collected retrospectively to gather clinical information including clinical factors, tumor-related factors and surgery-related factors. In patients with autologous blood storage, preoperative Hb was indicated as Hb before the storage. The surgical procedure was selected based on the extent of the tumor and residual liver function. The indication for surgery and selection of surgical procedure were not different between period A and period B. The histological grade of differentiation of HCC was determined according to the Edmondson-Steiner classification, and was based on the areas of the tumor with the highest grade[18]. Data were expressed as mean ± standard deviation. Differences between groups were assessed by the chi-square test, Fisher's exact test or the Mann-Whitney *U* test. Survival rates were calculated according to the Kaplan-Meier method, and compared using the log-rank test. Multivariate logistic regression analysis was performed for the selection of significant variables. Statistical analysis was performed using StatView (version 5.0; SAS Institute Inc., Cary, NC). A P value < 0.05 was considered significant. The study protocol was approved by the Human Ethics Review Committee of Osaka University Hospital and a signed consent form was obtained from each patient.

RESULTS

Table 1 shows the clinicopathological characteristics of patients in period A (n = 93) and in period B (n = 201). The clinical features, tumor-related features, and surgery-related factors were not significantly different between patients of the 2 groups. HT was administered in 56 of the 93 patients (60.2%) in period A. In period B, HT was administered in 38 patients (18.9%) (HT group), AT in 134 patients (66.7%), and neither AT nor HT in 45 patients (22.4%) (non-transfusion group). In 134 AT patients, the amount of transfused autologous blood was 200 mL in 3 patients, 400 mL in 63 patients, 600 mL in 2 patients, 800 mL in 62 patients, 1000 mL in 1 patient, and 1200 mL in 3 patients. Among the 134 patients with AT, only AT was administered in 118 patients (58.7%) (AT group), and both AT and HT in the remaining 16 patients (8.0%). Figure 1 shows the distribution of patients according to blood transfusion. Thus, the proportion of patients who received HT was significantly lower in period B than in period A (P < 0.0001). With regard to disease-free survival examined only in patients with curative surgery for HCC, there were no significant differences between period A and period B; the 1-, 3-, 5-, and 10-year disease-free survival rates were 73.9%, 39.5%, 24.7%, and 7.2% for patients in period A, and 65.9%, 34.8%, 21.9%, and 7.2% for patients in period B (P = 0.5688), respectively. The 1-, 3-, 5- and 10-year overall survival rates were 85.7%, 75.6%, 63.1%, and 28.5% for patients in period A, and 92.9%, 70.6%,

Table 1 Clinicopathological characteristics of patients of periods A and B with hepatocellular carcinoma

	Period A (1991-1994) (*n* = 93)	Period B (1995-2000) (*n* = 201)	*P*-value
Clinical factors			
Gender (male/female)	81/12	161/40	0.144
Age (yr)[1]	61 ± 9	62 ± 9	0.102
HBs-Ag (±)	73/20	169/32	0.243
Anti-HCV Ab (±/unknown)	29/62/2	71/125/5	0.471
Child-Pugh classification (A/B)	79/14	160/41	0.275
Preoperative Hb (g/dL)[1]	13.6 ± 1.5	13.3 ± 1.6	0.213
Tumor-related factors			
Number of tumors (single/multiple)	70/23	146/55	0.635
Maximum tumor size (cm)[1]	3.8 ± 2.7	4.1 ± 3.1	0.450
Vascular invasion (±)	83/10	172/29	0.388
Histological grade (Ⅰ, Ⅱ/Ⅲ, Ⅳ/unknown)	40/41/12	89/92/20	0.975
Surgery-related factors			
Procedure (nonanatomical/anatomical)	45/48	101/100	0.767
Operation time (min)[1]	291 ± 144	295 ± 151	0.853
Resected liver volume (g)[1]	218 ± 406	214 ± 289	0.925
Intraoperative blood loss (mL)[1]	2190 ± 5689	1621 ± 2209	0.219

[1]Data are expressed as number of patients and mean ± standard deviation. HBs-Ag: Hepatitis B surface antigen; Anti-HCV Ab: Anti-hepatic C virus antibody; Hb: Hemoglobin.

Table 2 Clinicopathological characteristics of patients with hepatocellular carcinoma according to homologous blood transfusion

	Non-HT group (*n* = 200)	HT group (*n* = 94)	*P*-value
Clinical factors			
Gender (male/female)	162/38	80/14	0.390
Age (yr)[1]	62 ± 9	60 ± 9	0.084
HBs-Ag (±)	168/32	74/20	0.269
Anti-HCV Ab (±/unknown)	65/130/5	35/57/2	0.437
Child-Pugh classification (A/B)	167/33	72/22	0.157
Preoperative Hb (g/dL)[1]	13.5 ± 1.6	13.2 ± 1.7	0.171
AT administration (±)	82/118	78/16	< 0.0001
Tumor-related factors			
Number of tumors (single/multiple)	149/51	67/27	0.559
Maximum tumor size (cm)[1]	3.6 ± 2.4	4.9 ± 3.7	0.000
Vascular invasion (±)	177/23	78/16	0.193
Histological grade (Ⅰ, Ⅱ/Ⅲ, Ⅳ/unknown)	91/88/21	38/45/11	0.446
Surgery-related factors			
Procedure (nonanatomical/anatomical)	111/89	35/59	0.004
Operation time (min)[1]	264 ± 130	356 ± 166	< 0.0001
Resected liver volume (g)[1]	159 ± 196	336 ± 490	< 0.0001
Intraoperative blood loss (mL)[1]	993 ± 707	3522 ± 6104	< 0.0001

[1]Data are expressed as number of patients and mean ± standard deviation. HBs-Ag: Hepatitis B surface antigen; Anti-HCV Ab: Anti-hepatic C virus antibody; Hb: Hemoglobin; AT: Autologous transfusion; HT: Homologous transfusion.

58.2%, and 40.3% for patients in period B ($P = 0.3202$).

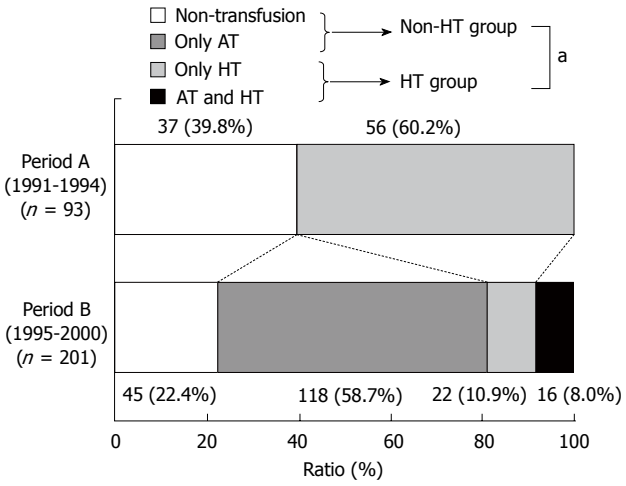

Figure 1 Distribution of patients according to transfusion status during periods A and B. The proportion of patients who received HT was significantly lower in period B than period A ([a]$P < 0.0001$). AT: Autologous transfusion; HT: Homologous transfusion.

In order to identify the factors that can predict the need for HT, various clinical parameters, tumor-related factors, and surgery-related factors were compared between the non-HT group and the HT group (Table 2). The preoperative Hb level was not significantly different between the 2 groups (13.5 ± 1.6 g/dL *vs* 13.2 ± 1.7 g/dL, $P = 0.1708$). The proportion of patients who received AT was significantly lower in the HT group than the non-HT group [59.0% (118/200) *vs* 17.0% (16/94), $P < 0.0001$]. The maximum tumor size was significantly larger in the HT group than in the non-HT group (4.9 ± 3.7 cm *vs* 3.6 ± 2.4 cm, $P = 0.0003$). As for surgery-related factors, there were significant differences in surgical procedure ($P = 0.0035$), operation time ($P < 0.0001$), resected liver volume ($P < 0.0001$), and intraoperative blood loss ($P < 0.0001$), suggesting that surgery in the HT group was major compared to that in the non-HT group.

To identify significant factors that could predict the need for HT, multivariate logistic regression analysis was performed (Table 3). The analysis was carried out using the 6 significant factors identified in the comparison of the non-HT group and the HT group. The analysis identified AT administration, intraoperative blood loss, and resected liver volume as significant independent predictors for the need of HT ($P < 0.0001$, $P < 0.0001$, $P = 0.0362$, respectively). Long-term postoperative outcome after surgery for HCC was examined. In this analysis, patients were limited to those with curative resection, which was defined as complete removal of all macroscopically evident tumors [non-HT group: 193 patients (non-transfusion group: 78 patients; AT group: 115 patients), HT group: 83 patients]. Among the 276 patients, 37 patients (13.4%) were followed-up for more than 10 years. The clinicopathological features of the groups are shown in Table 4. First, we compared the long-term postoperative outcome between the non-transfusion group and the AT group. The preoperative Hb level was significantly higher in the AT group than in the non-

Table 3 Results of multivariate logistic regression analysis for the need for homologous blood transfusion

		OR	95% CI	*P*-value
AT administration	±	28.571	9.615-83.333	< 0.0001
Maximum tumor size (cm)	< 5/≥ 5	1.126	0.500-2.538	0.774
Procedure	Nonanatomical/anatomical	1.016	0.449-2.202	0.967
Operation time (min)	< 300/≥ 300	0.986	0.435-2.242	0.974
Resected liver volume (g)	< 200/≥ 200	2.532	1.062-6.061	0.036
Intraoperative blood loss (mL)	< 2000/≥ 2000	30.303	9.346-100.000	< 0.0001

OR: Odds ratio; CI: Confidence interval; AT: Autologous transfusion.

Table 4 Clinicopathological characteristics of patients who underwent curative surgery for hepatocellular carcinoma

	Non-HT group (*n* = 193)	HT group (*n* = 83)	*P*-value (Non-HT *vs* HT)	Non-HT group		
				Non-transfusion group (*n* = 78)	AT group (*n* = 115)	*P*-value (Non-transfusion *vs* AT)
Clinical factors						
Gender (male/female)	156/37	70/13	0.488	63/15	93/22	0.986
Age (yr)[1]	62 ± 8	61 ± 9	0.115	62 ± 8	61 ± 9	0.878
HBs-Ag (±)	163/30	67/16	0.445	Nov-67	96/19	0.649
Anti-HCV Ab (±/unknown)	62/127/4	31/51/1	0.426	21/54/3	41/73/1	0.254
Child-Pugh classification (A/B)	161/32	65/18	0.262	66/12	95/20	0.833
Preoperative Hb (g/dL)[1]	13.5 ± 1.5	13.4 ± 1.6	0.425	12.8 ± 1.8	14.1 ± 1.1	< 0.0001
Tumor-related factors						
Number of tumors (single/multiple)	147/46	64/19	0.866	62/16	85/30	0.372
Maximum tumor size (cm)[1]	3.5 ± 2.4	4.8 ± 3.7	0.000	3.3 ± 2.2	3.6 ± 2.4	0.287
Vascular invasion (±)	172/21	70/13	0.268	73/5	99/16	0.101
Histological grade (Ⅰ, Ⅱ/Ⅲ, Ⅳ/unknown)	89/83/21	33/41/9	0.304	36/34/8	53/49/13	0.412

[1]Data are expressed as number of patients and mean ± standard deviation. HBs-Ag: Hepatitis B surface antigen; Anti-HCV Ab: Anti-hepatic C virus antibody; Hb: Hemoglobin; AT: Autologous transfusion; HT: Homologous transfusion.

transfusion group (14.1 ± 1.1 g/dL *vs* 12.8 ± 1.8 g/dL, $P < 0.0001$). Tumor-related factors were similar in the 2 groups. There were no significant differences in the disease-free survival rates between the AT group (1-, 3-, 5-, and 10-year: 70.6%, 37.1%, 22.3%, and 11.2%, respectively) and the non-transfusion group (73.1%, 41.3%, 30.7%, and 9.6%, respectively) ($P = 0.3874$) (Figure 2A). Next, we compared the long-term survival rates of the non-HT group and the HT group. Although the cumulative disease-free survival rate of the non-HT group was significantly better than that of the HT group ($P = 0.0305$) (Figure 2B), since the maximum tumor size was significantly different in the comparison (3.5 ± 2.4 cm *vs* 4.8 ± 3.7 cm, $P = 0.0004$), additional comparison was also performed based on the tumor size. The disease-free survival rates for the non-HT group (1-, 3-, 5-, and 10-year: 75.6%, 42.6%, 29.4%, and 10.8%, respectively) was significantly better than those of the HT group (69.0%, 31.6%, 16.7%, and 4.5%, respectively) of the subgroup with tumor size 5.0 cm or smaller than 5.0 cm ($P = 0.0452$) (Figure 2C), but not in patients with tumor size larger than 5.0 cm (1-, 3-, 5-, and 10-year: 56.4%, 24.1%, 10.8%, and 5.4% in the non-HT group, and 39.4%, 26.3%, 13.1%, and 0.0% in the HT group, respectively, $P = 0.7391$) (Figure 2D). Furthermore, multivariate analyses using significant factors identified in the univariate analyses demonstrated that transfusion status (non-HT/HT) was one of the independent significant factors for disease-free survival ($P = 0.0380$) (Table 5), suggesting disadvantages of HT on postoperative prognosis.

DISCUSSION

The results of the present study demonstrated a reduction in HT administration in surgery for HCC after the introduction of AT. Our results are in agreement with those of previous reports which emphasized the significance of AT in reducing the need for HT in surgery for HCC[16,17]. However, in these previous reports, only 20-30 patients were included in the AT group. Furthermore, although the Hb level immediately before surgery was reported in the AT group, the Hb level before storage was not indicated, suggesting a different clinical background of patients who received HT and those of other groups. On the other hand, in the present study, despite its retrospective design, the clinicopathological background, including the Hb level, was similar in the 2 groups as shown in Table 1. In this regard, the present study is significant as it identified the benefits of AT in the reduction of HT administration.

In the present study, we analyzed the data for significant predictors of HT use. The results showed that AT administration was an independent significant predictor of the need for HT, and support the significance of AT in reducing the need for HT. In the analysis, preoperative Hb, which is reported to be significantly associated with the need for HT[19,20], was not an independent significant factor. While the reason for this difference in the results

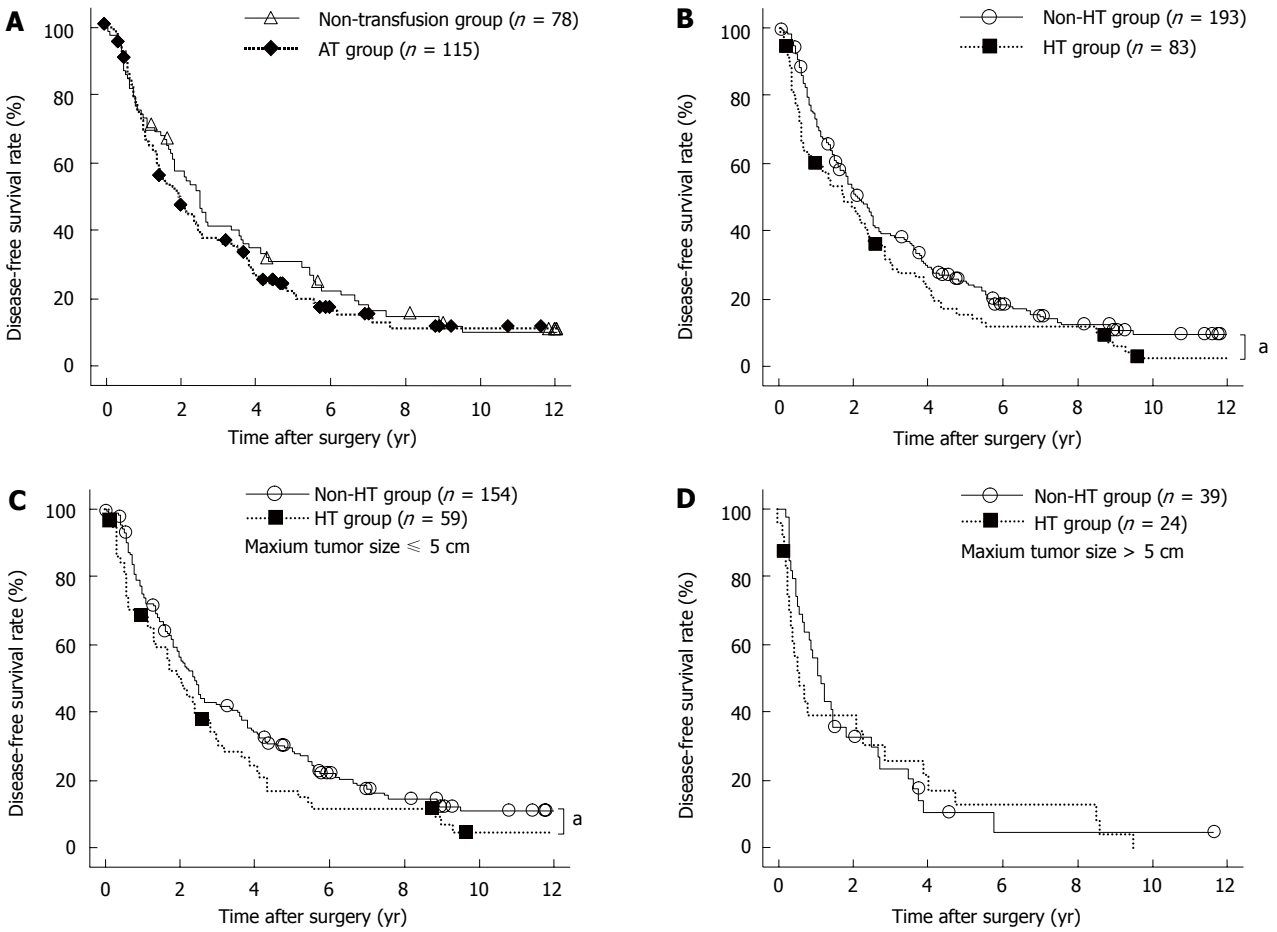

Figure 2 Disease-free survival after curative surgery for hepatocellular carcinoma. A: There were no significant differences between the non-transfusion group (solid line) and the Autologous transfusion (AT) group (dotted line) (P = 0.3874); B: The cumulative disease-free survival in the non-Homologous transfusion (HT) group (solid line) was significantly better than in the HT group (dotted line) (^aP = 0.0305); C: The disease-free survival in the non-HT group (solid line) was significantly better in than the HT group (dotted line) in patients with maximum tumor size of ≤ 5.0 cm (^aP = 0.0452); D: No significant differences were noted between the non-HT group (solid line) and the HT group (dotted line) in patients with the maximum tumor size > 5.0 cm (P = 0.7391).

Table 5 Statistical analysis of disease-free survival of patients with curative resection for hepatocellular carcinoma

	Univariate		Multivariate	
	P-value	OR	95% CI	*P*-value
Clinical factors				
Gender (male/female)	0.840			
Age (yr) (≤ 63/> 63)	0.402			
HBs-Ag (±)	0.279			
Anti-HCV Ab (±)	0.045	1.401	1.032-1.901	0.031
Child-Pugh classification (A/B)	0.079			
Preoperative Hb (g/dL) (≤ 12/> 12)	0.824			
Transfusion (non-HT group/HT group)	0.031	1.372	1.018-1.849	0.038
Tumor-related factors				
Number of tumors (single/multiple)	0.000	1.819	1.290-2.564	0.001
Maximum tumor size (cm) (≤ 5/> 5)	0.001	1.07	0.750-1.525	0.709
Vascular invasion (±)	< 0.0001	2.473	1.606-3.806	< 0.0001
Histological grade (Ⅰ, Ⅱ/Ⅲ, Ⅳ)	0.017	1.188	0.898-1.570	0.227

OR: Odds ratio; CI: Confidence interval; HBs-Ag: Hepatitis B surface antigen; Anti-HCV Ab: Anti-hepatic C virus antibody; Hb: Hemoglobin; HT: Homologous transfusion.

remains unclear, it could be due to the effect of recombinant human erythropoietin administered after the storage of autologous blood. Alternatively, it is possible that, since the subjects of the above previous studies did not receive AT, the significance of preoperative Hb is overestimated. Thus, the present study is significant in terms of identifying the effect of AT in reducing HT using appropriate statistical analysis.

We also investigated the effects of AT and HT on postoperative outcome after curative surgery for HCC. The study revealed that the disease-free survival rates were comparable between the non-transfusion group and the AT group when the clinical background was similar. Furthermore, the disease-free survival rates of the HT group were significantly worse than those of the non-HT group, based on the results of univariate analysis. Since there was a significant difference in the maximum tumor size between the 2 groups, which suggests the possibility of different tumor biology and recurrences between the HT group and the non-HT group, the survival rate was compared in subgroups based on tumor size, and showed significant differences in the pa-

tients with tumor size ≤ 5.0 cm. In addition, the difference was confirmed to be independently significant by multivariate analyses.

Since the report of a survival advantage of HT in patients undergoing colectomy for colon cancer[21], some investigators have indicated that HT triggers recurrence in various kinds of cancers[6-8]. This HT-induced disadvantage is speculated to be derived from transfusion-associated immunomodulation. Actually, several investigators suggested that HT induces downregulation of natural killer cell activity and cytotoxic T-cell function, resulting in a subclinical state of anergy or tolerance[22-24].

The correlation has been reported also in patients with HCC[9-14,25]. Although the results of the present study were comparable to these previous reports, we think that the present study reports a new finding based on the inclusion of patients who were followed-up for more than 10 years. With regard to the long-term survival advantages, to our knowledge, there are only a few reports describing the survival advantage of HT on long-term prognosis (> 10 years). Hirano *et al*[14] investigated the long-term (> 10 years) survival disadvantage of HT over AT, but their reports did not include the clinical background of patients and described the results of only univariate analysis, suggesting inadequate analysis. Also in this regard, the present study provides significant data.

Thus, the present study revealed that AT is significant in reducing the need for HT, which is associated with a long-term postoperative survival disadvantage after HCC surgery. In this study, however, in order to investigate the long-term postoperative outcome for more than 10 years, we limited inclusion in the study to patients who underwent surgery between 1991 and 2000. Based on this limitation, it is possible that the selected time period does not reflect recent advances in both surgical and anesthetic techniques, which could explain the recent decrease in intraoperative blood loss. Considering such recent advances affecting intraoperative blood loss, one can speculate that there are increasingly more patients with HCC who do not need AT. It was also reported recently that the practice of using autologous blood requires more administrative work and laborious collection procedures, and is not without disadvantages[26-29]. Taken together, AT actually has advantage an over HT, but currently, it may be necessary to deliberate on the need for AT itself during surgery for HCC.

In summary, the present study showed that AT administration significantly decreased the need for HT in surgery for HCC, and that AT was one of the significant independent predictor of the need for HT. Considering that HT was disadvantageous with regard to long-term postoperative survival, one can assume that AT administration can lead to improvement in the long-term postoperative outcome of patients with HCC.

COMMENTS

Background

Some evidences suggest that homologous blood transfusion (HT) may be adversely associated with tumor recurrence and poor survival in various kinds of cancers, and autologous blood transfusion (AT) is currently used for patients scheduled for surgery. To date, several investigators have examined the significance of AT in terms of reducing the need for HT and postoperative outcome, but few were conducted with proper statistical analyses to identify the significance of AT in surgery for hepatocellular carcinoma (HCC).

Research frontiers

The authors compared the proportion of patients who received HT between 2 groups determined by the time of AT introduction; period A (1991-1994, *n* = 93) and period B (1995-2000, *n* = 201), and performed multivariate logistic regression analysis for identification of independent significant predictors of the need for HT. Furthermore, they investigated the impact of AT and HT on long-term postoperative outcome after curative surgery for HCC.

Innovations and breakthroughs

The present study showed that the proportion of patients having HT was decreased after AT introduction, that AT administration was a significant independent predictor of the need for HT, and identified HT administration as an independent significant factor for poorer disease-free survival.

Applications

Considering the results of the present study, it could be suggested that AT administration could improve the long-term outcome of patients with HCC.

Peer review

This is a large series of patients treated in several ways with respect to the need for blood transfusion during their surgery for HCC. Unfortunately the authors have a mix of numbers that they have used in different ways to make the conclusion they wanted to make.

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