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Long-Term Safety of Autotransfusion During Hepatectomy for Hepatocellular Carcinoma

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Abstract

Purpose. To evaluate the long-term safety of autotransfusion (AT) in hepatectomy for hepatocellular carcinoma (HCC).

Methods. Between 1988 and 1989, 46 patients with HCC underwent hepatectomy with AT (group 1). For a comparison, we matched 50 patients with HCC who underwent hepatectomy, and received homologous but not autologous blood (group 2). The 10-year cumulative survival curves and cancer-free curves of the two groups were examined, and the pattern of recurrence was compared.

Results. Group 1 had a significantly higher cumulative 10-year survival rate than group 2, at 20% vs 8%, respectively ($P < 0.05$). Among the patients who underwent curative resection, those in group 1 had significantly better cumulative survival and cancer-free survival rates than those in group 2, at 27% vs 11% ($P < 0.05$) and 13% vs 0% ($P < 0.05$), respectively. Among the patients with stage I–II HCC, those in group 1 had significantly better cumulative survival and cancer-free survival rates than those in group 2, at 30% vs 5% ($P < 0.01$) and 20% vs 5% ($P < 0.05$), respectively. However, the rates were similar among patients with stage III–IV disease in both groups. The pattern of recurrence in the two groups was similar.

Conclusion. Autotransfusion promoted survival in patients undergoing hepatectomy for stage I or II HCC.

Key words Autotransfusion · Hepatocellular carcinoma · Hepatectomy

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Introduction

Hepatectomy for hepatocellular carcinoma (HCC) usually requires intraoperative transfusion because of the complicated vascular anatomy and concomitant cirrhosis. Despite improved safety, homologous transfusion (HT) is still associated with a risk of infection and graft-versus-host disease. Moreover, we and others have reported that HT may adversely affect the prognosis of patients undergoing hepatectomy.[1–6] Autologous transfusions (AT), provided by preoperative blood donation and intraoperative blood salvage, have been developed as a strategy to reduce the need for homologous blood. Thus, it is now possible to perform hepatectomy using little or no homologous blood.

In January 1988, we started a program of AT for patients undergoing hepatectomy for HCC. We reviewed the clinical data of 46 patients who received AT, and matched them with the data of 50 patients who received HT between September 1986 and December 1987. We previously reported clinical data 3 years after hepatectomy showing that AT is safe and effective,[1,2] and we now present evidence of the beneficial effects of intraoperative AT, 10 years after hepatectomy for HCC.

Patients and Methods

Patients

Our original AT study included 54 patients with HCC who underwent hepatectomy between January 1988 and April 1989. We were able to follow up 46 of these patients completely for 10 years after surgery (group 1). The patients in group 1 were matched for comparison with 50 patients with who underwent hepatectomy for HCC, without AT, between September 1986 and December 1987, all of whom were also followed up for

10 years (group 2). All patients in the two groups were operated on by the same surgeon. The mean age was 58.4 years in group 1 ($n = 46$) and 57.2 years in group 2 ($n = 50$). The sex distribution was also similar, with 89.1% of group 1 and 84.3% of group 2 being men. The macroscopic disease staging in groups 1 and 2, respectively, was as follows: stage I, 2.2% and 7.6%; stage II, 41.3% and 34.6%; stage III, 32.6% and 28.9%; and stage IV, 23.9% and 28.9%. Curative resection was done in 23 patients (50%) in group 1 and in 28 patients (56%) in group 2. There were no significant intergroup differences in clinical background, including age, sex, clinical stage, or curative resection rate.

Autologous Transfusion Programs

Blood for AT was collected preoperatively from all patients in group 1, followed by intraoperative blood salvage. The preoperative blood donation was carried out according to the autologous blood donation program as reported before. Each patient donated 200–400 ml of blood weekly to a total volume of 400–1000 ml, as long as their hemoglobin concentration was ≥11 mg/dl before each blood donation.

The Haemonitics cell saver (Haemonitics, Braintree, MA, USA) was used as the intraoperative blood salvager. The AT device was used with the consent of the patient, in anticipation of intraoperative blood loss, and because it was available and relatively inexpensive. The cell saver program is described in our previous report.[1]

Fresh frozen plasma was given to most of the patients in group 2 as a volume replacement solution and as a coagulation factor replacement. Fresh frozen plasma was not used for this purpose in group 1. Instead, crystalloid, colloid containing albumin, was used for volume replacement in this group.

Blood Loss and Blood Usage

There was no significant difference in the mean blood loss between groups 1 and 2, at 1989 ml vs 1752 ml. In group 1, 15 patients underwent hepatectomy with AT and no HT. The mean volume of AT blood was 856 ml; 467 ml from preoperative donation, and 389 ml from intraoperative salvage. The mean total volume of homologous transfusion was 921 ml; 757 ml from packed red blood cells or whole blood, and 164 ml of FFP. In contrast, 49 patients in group 2 required a large volume of homologous blood, as 1602 ml packed red blood cells or whole blood, and 1864 ml of FFP. There was a significant difference in the mean volume of HT between groups 1 and 2 ($P < 0.05$).

Statistical Analysis

Comparisons of mean levels were made with the Wilcoxon Rank Sum test. Life-table analyses are presented as Kaplan–Meier plots. The generalized Wilcoxon test was used to determine if there were significant differences between the curves. All tests were two-tailed, and differences were considered significant at $P < 0.05$.

Results

Long-Term Outcome After Hepatectomy

Figure 1A shows the cumulative survival curves in groups 1 and 2. The 10-year cumulative survival rates were 20% in group 1 (the autotransfused group) and 8% in group 2 (the non-autotransfused group). The patients who did not receive AT had significantly poorer survival than those who did receive AT ($P < 0.05$). In contrast, no significant difference was seen between the groups in 10-year cumulative cancer-free survival rates. All deaths were caused by recurrence of the original cancer.

Among the patients who underwent curative resection, the 10-year cumulative survival rates were 27% in group 1 and 11% in group 2 (Fig. 1B). The 10-year cumulative cancer-free survival rates were 13% in group 1 and 0% in group 2. Group 2 had significantly lower cumulative survival rates and cumulative cancer-free survival rates than group 1 ($P < 0.05$).

We then examined the 10-year survival rates in patients with stage I–II disease and those with stage III–IV disease (Fig. 1C,D). The patients with stage I–II disease in group 2 had significantly lower cumulative and cancer-free survival rates than those in group 1 ($P < 0.05$). No significant intergroup difference was identified in survival rates in the stage III–IV patients between the two groups.

Patterns of Initial Recurrence and Distal Metastasis

Intrahepatic recurrence developed in 37 (88.1%) patients in group 1 and 48 (96%) in group 2. In group 1, recurrence was managed by repeat resection in 2.7%, transarterial embolization (TAE) in 40.5%, TAE with percutaneous ethanol injection (PEI) in 18.9%, PEI in 24.3%, and other methods in 13.6%. In group 2, recurrence was managed by repeat resection in 2.1%, TAE in 31.3%, TAE with PEI in 14.6%, PEI in 18.8%, and other methods in 33.1%. The pattern of initial recurrence in the liver was investigated whenever possible. The rate of multiple recurrences was higher in group 2 than in group 1 (60% vs 40%), but not significantly. The effect of the Haemonitics cell saver on recurrence also

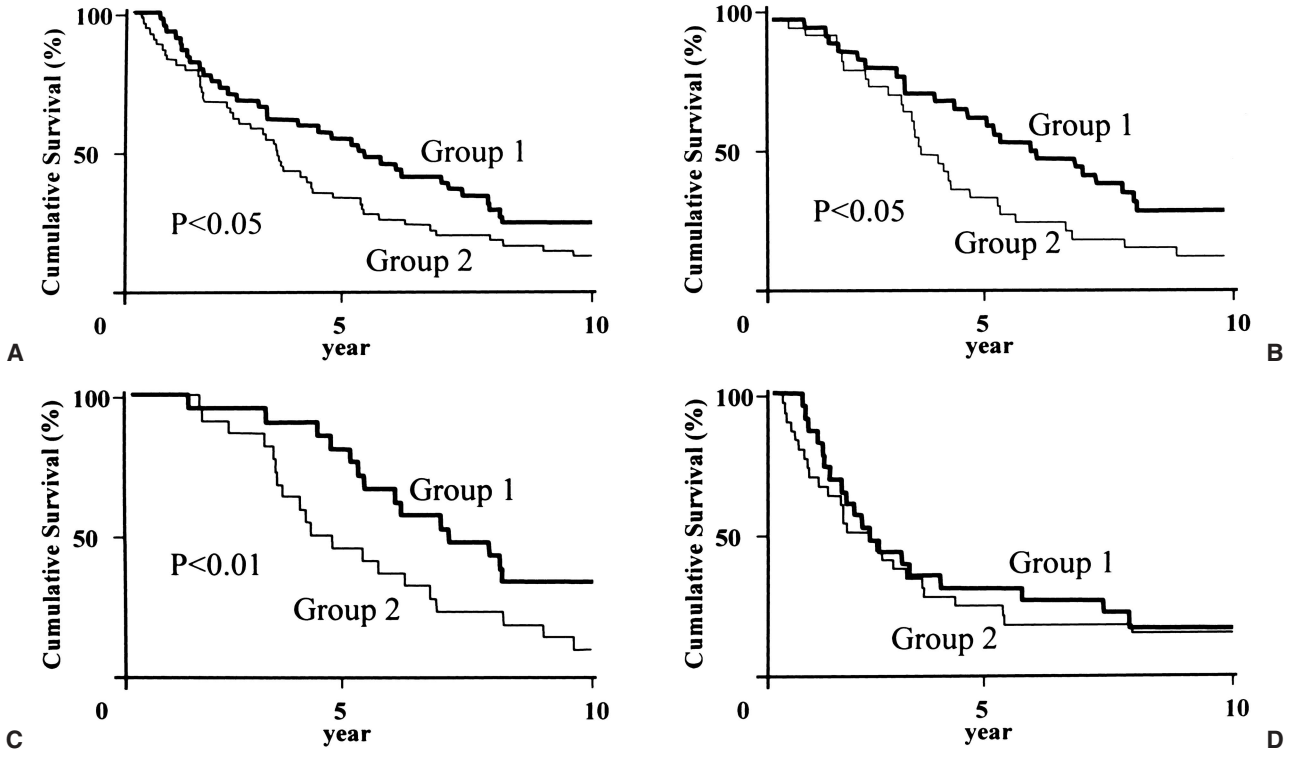

Fig. 1. **A** Cumulative survival rates after resection of hepatocellular carcinoma. A significant difference was noted between group 1 (*bold line*, $n = 46$) and group 2 (*fine line*, $n = 50$) ($P < 0.05$). **B** Cumulative survival curves in patients who underwent curative resection. A significant difference was noted between group 1 (*bold line*, $n = 32$) and group 2 (*fine line*, $n = 31$) ($P < 0.05$). **C** Cumulative survival curves in patients with early-stage hepatocellular carcinoma (stage I–II). A significant difference was noted between group 1 (*bold line*, $n = 22$) and group 2 (*fine line*, $n = 21$) ($P < 0.01$). **D** Cumulative survival curves in patients with stage III–IV hepatocellular carcinoma. No significant difference was noted between group 1 (*bold line*, $n = 24$) and group 2 (*fine line*, $n = 29$)

was examined. The pattern of initial recurrence among patients in group 1 was not affected by the use of the cell saver.

We also examined the incidence of distant metastases (Table 1). Distant metastasis developed in 12 (26.1%) patients in group 1 (lung, 7; bone, 3; adrenal gland, 1; skin, 1) and in 16 (32%) patients in group 2 (lung, 6; bone, 7; brain, 1; adrenal gland, 1; skin, 1). The differences between the groups were not significant.

Table 1. Comparison of distal metastasis after hepatectomy with and without homologous blood transfusion

	No. of patients	
	Group 1	Group 2
Brain		1
Lung	7	6
Bone	3	7
Adrenal gland	1	1
Skin	1	1
Total	12	16

Discussion

Our autologous blood program, with intraoperative blood salvage and preoperative blood donation, reduced the volume of banked blood needed and improved the prognosis of patients undergoing hepatectomy for HCC. Homologous transfusion was found to induce immunosuppression in renal transplantation;[7,8] therefore, the advantages of AT extend beyond the risks of transfusion itself as it improves prognosis after surgery for malignant diseases by preventing immunosuppression. Following the initial report by Foster et al.[9] of a survival advantage in patients undergoing colectomy for colon cancer, several other reports have shown that HT triggers the recurrence of certain cancers.[10–14] This phenomenon has also been reported in patients undergoing hepatectomy for HCC.[2–6] To our knowledge, the present study is the first to provide evidence that a survival advantage exists for at least 10 years in patients with early (stage I–II), but not late (stage III–IV) HCC. A similar result in patients with early-stage

HCC was reported by Asahara et al.[6] Although the pathogenesis responsible for immunosuppression remains unclear, several reports have identified decreases in the CD4/CD8 ratios[15,16] and natural killer (NK) cell activity.[17,18] We also participated in a multi-institutional nationwide survey on the efficacy of AT and postoperative cell-mediated immunity in patients with gastrointestinal cancer. In this report, postoperative changes in the values of cellular immunity parameters were compared among an AT group, an HT group, and a no-transfusion (NT) group. The results of this study showed a depression of NK activity 1–2 weeks postoperatively in all groups. However, this depression tended to be reversed by week 3 in the AT and NT groups, whereas it was significantly greater with no such recovery in the HT group.[19] These immune systems are part of the first line of defense against malignant tumor growth. Homologous transfusion may compromise the immunologic competence of the host and allow residual tumor cells to establish themselves, especially in patients with early-stage malignant disease.

Despite its advantages, AT (especially intraoperative blood salvage) was initially considered to be contraindicated in cancer surgery because of the risk of systemic dissemination of tumor cells. This bias was introduced by Yaw et al.[20] who showed that tumor cells in processed blood passed through filters in the Bentley autotransfusion device. However, the Haemonitics cell saver processes blood by centrifuged-based washing after filtration. Thus, the risk of reinfusion of malignant cells is lower with the Haemonitics system than with the Bentley system. We and others have since demonstrated the safety of the cell saver in experimental and clinical studies.[21,22] The similarity in the pattern of initial recurrence and distal metastasis in patients who received AT and those who did not is further evidence of its safety.

Preoperative blood donation (POD) has become a widely accepted practice before surgery for malignant disease. Although there was initial concern that cancer cells in the donated blood might produce metastasis after infusion, the safety of POD has been confirmed by several studies. Yoshida et al.[23] reported that tumor cells lost activity within 24 h in CPD fluid. Furthermore, Kitagawa et al.[24] analyzed blood samples from patients with HCC for α-fetoprotein (AFP) mRNA using reverse transcription–polymerase chain reaction and found no AFP mRNA in any sample stored for longer than 14 days. These reports show that tumor cells in stored blood become inactive and lose their potential during storage.

Recent improvements in liver surgery, including full vascular isolation of the liver, intermittent clamping of the portal pedicle, and the use of an ultrasonic surgical aspirator, have greatly reduced blood loss during major hepatic resection. In addition, the availability of recombinant human erythropoietin (rh-EPO) has further reduced the need for homologous transfusion.[25] We currently use AT for all patients who undergo hepatectomy, and administer rh-EPO 6000 IU intravenously three times a week preoperatively to patients whose hemoglobin concentration is less than 13 g/dl. Consequently, more than 60% of patients do not require HT intraoperatively, even though most of them have cirrhosis or chronic hepatitis.

Our data provide further evidence of the long-term safety of AT in patients with HCC undergoing hepatectomy. Moreover, reducing the need for HT by AT improves the long-term prognosis of patients undergoing hepatic resection for early HCC.

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