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Controversy over the use of intraoperative blood salvage autotransfusion during liver transplantation for hepatocellular carcinoma patients

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Abstract

Intraoperative blood salvage autotransfusion (IBSA) is used in various surgical procedures. However, because of the risk of reinfusion of salvaged blood contaminated by tumor cells, the use of IBSA in hepatocellular carcinoma (HCC) patients undergoing liver transplantation (LT) is controversial. The critical points include whether tumor cells can be cleared by IBSA, whether IBSA increases the risk of recurrence or metastasis, and what are the indications for IBSA. Moreover, is it warranted to take the risk of tumor dissemination by using IBSA to avoid allogeneic blood transfusion? Do the remaining tumor cells after additional filtration by leukocyte depletion filters still possess potential tumorigenicity? Does IBSA always work well? We have reviewed the literature and tried to address these questions. The available data indicate that IBSA is safe in LT for HCC, but randomized, controlled and prospective trials are urgently required to clarify the uncertainty.

Key words: Intraoperative blood salvage autotransfusion; Liver transplantation; Hepatocellular carcinoma; Leukocyte depletion filters; Allogeneic blood transfusion

Core tip: The use of intraoperative blood salvage autotransfusion (IBSA) in hepatocellular carcinoma (HCC) patients undergoing liver transplantation is controversial as it may reinfuse salvaged blood contaminated by tumor cells. In this article, we reviewed the relevant literature and tried to address the critical questions about IBSA. The available data indicate that IBSA is safe in liver transplantation for HCC, but randomized, controlled and prospective trials are urgently required to clarify the uncertainty.

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COMMENTARY ON HOT TOPICS

We have read with great interest the recent article by Akbulut *et al*[1] describing the effects of intraoperative blood salvage autotransfusion (IBSA) during liver transplantation (LT) in patients with hepatocellular carcinoma (HCC) on tumor recurrence or metastasis, and would strongly recommend it to the readers.

HCC is often associated with chronic hepatitis B and C, particularly in East and Southeast Asia, Middle and Western Africa, and Northern and Eastern Europe, where as high as 85% of HCC patients simultaneously suffer from liver cirrhosis[2]. In view of the impaired liver function, elevated portal pressure and increased collateral circulation in these patients, LT has been recommended

as an optimal treatment for HCC as the tumor burden and the underlying liver disease are resolved at the same time[3]. However, the decreased synthesis of coagulation factors, elevated portal pressure and increased collateral circulation all increase the risk of hemorrhage during surgery. Intraoperative hemorrhage is currently recognized as a mortality risk and massive blood transfusion is necessary during LT[4].

As a result of the underlying risk of transfusion of banked blood, IBSA has been used in various surgery procedures[5,6]. With this technique, blood lost during surgery is recovered and processed through a pump system called cell saver, then transfused back into the patient[7]. This requires a system that suctions the wound, separates the blood cells from the other blood products and debris, washes the cells, and returns them to the patient[1]. It is estimated that IBSA reduces the intraoperative blood requirement by up to 60%[1]. The main complication is dilutional or disseminated coagulopathy[8,9]. Another rare complication is pulmonary injury probably linked to leukoagglutinins and transient hemoglobinuria[10]. At present, the risk of complications during IBSA has declined due to technical advances, and IBSA has significantly lower adverse events than allogeneic blood transfusion[11]. However, the use of IBSA in surgical oncology involving LT in HCC patients is controversial, as it may result in reinfusion of salvaged blood contaminated by tumor cells[11]. To date, a few studies have investigated the effects of IBSA system on tumor recurrence in HCC patients undergoing LT[4,6,11].

Can tumor cells be filtered away by IBSA?

The process of IBSA involves collection of blood, filtration, washing, and reinfusion. The use of IBSA for cancer patients is always performed with caution as blood collected from the operating site is at a high risk of contamination with tumor cells. Tumor cells are detected in 91%-93% of blood samples from surgical sites during various cancer surgical procedures including liver resection for liver metastasis[12,13]. During LT for HCC patients, the detection rate of tumor cells in samples from surgical sites was as high as 62.5%[6]. Moreover, Hansen *et al*[13] has reported that in one-third of cases examined, tumor cells in blood collected from surgical sites showed proliferative capacity by forming cell colonies, invasive capacity by passing the collagen coated membrane *in vitro*, and one cell line displayed tumorigenicity *in vivo*, indicating the underlying hazards of salvaged blood.

The crucial consideration is whether IBSA can effectively filter out the tumor cells. Obviously, the use of IBSA alone is not satisfactory, as tumor cells are detected in 62%-91.2% of blood samples after filtration[6,11,14,15]. Leukocyte depletion filters (LDF) with smaller-diameter (3-8 μm) holes have been recommended to further clear away tumor cells from the collected blood. The high efficacy of LDF in removing tumor cells from blood collected from surgical sites has been reported in patients with HCC and prostate, bladder, lung, breast, endometrial, cervical and ovarian cancers[11,14-18]. Catling *et al*[15] reported that LDF removed all the tumor cells in 91.2% of positive samples after LDF with IBSA. Considering the difference in diameters of tumor cells, Liang *et al*[6] further compared the positive cell rates by using the IBSA system with and without LDF in HCC patients undergoing LT, and the results showed that only 25% of the positive samples became negative after cell saver processing, while after additional filtration by LDF, only 2 out of 20 patients whose tumors were unexpectedly ruptured during surgery had the collected blood positive for α-fetoprotein mRNA, and one of these patients was still positive after the second LDF[6]. These data indicate that LDF can render IBSA more efficient in eliminating tumor cells from blood collected from surgical sites, and thus reduce the risk of tumor cell reinfusion.

Does IBSA increase the risk of recurrence or metastasis?

Although more evidence supports application of IBSA in surgical oncology, the fear of reinfusing tumor cells always troubles surgeons. However, in fact, a case report was the only evidence supporting the opinion up to now[19]. In 1975, a patient died from diffuse metastasis 4 wk after pneumonectomy. Because of the blood salvaged during surgery and tumor cells detected in salvaged blood, the metastasis was ascribed to the autotransfusion of blood[19]. Although the American Medical Association issued an alert about the use of IBSA in cancer surgery in 1986[11,15], some organizations, including the National Institute of Clinical Excellence, the Association of Anaesthetists of Great Britain and Ireland, the Obstetric Anaesthetists Association, the American College of Obstetricians and Gynecologists, and the British Confidential Enquiry of Maternal and Child Health have developed guidelines to support the use of IBSA alone or in combination with LDF in cancer surgery[11,15,20,21].

Notwithstanding the above facts, clinical investigations to clarify the correlation of IBSA with tumor recurrence or metastasis have been carefully conducted in the past few decades. The currently available results have failed to show that IBSA increases the risk of recurrence or metastasis; on the contrary, equivalent or even better outcomes have been reported in patients with various cancers who received IBSA during surgery[5,6,12,22-25].

A study aimed at evaluating the long-term safety of IBSA in hepatectomy for HCC was conducted by Hirano and collaborators[22]. Significantly higher 10-year cumulative overall survival and disease-free survival rates were demonstrated in the patients receiving IBSA, particularly patients with stage Ⅰ/Ⅱ HCC, but the differences in cumulative survival and cancer-free survival rates of patients with stage Ⅲ/Ⅳ HCC were not significant from those who did not receive IBSA[22]. Another study reported similar cumulative overall survival and recurrence rates in the IBSA group and IBSA-free group, but IBSA reduced the mean volume of infused allogeneic blood[26].

To date, three studies have investigated the use of IBSA in LT for HCC[4,6,11]. One was to evaluate the efficiency of additional LDF in eliminating tumor cells from IBSA[6]; the other two investigated whether IBSA

increased the risk of recurrence or metastasis[4,11]. In the study by Muscari *et al*[4], among the 47 HCC patients undergoing LT, 31 patients received IBSA while the other 16 did not. During a mean 34-mo follow-up period, both groups showed similar recurrence rates (6.4% in the IBSA group *vs* 6.3% in the IBSA-free group). In another study, Foltys *et al*[11] reported a similar recurrence rate and 5-year survival rate in the IBSA group of 40 patients compared with the IBSA-free group of 96 patients during a mean follow-up period of 1015 d. However, because the two studies lacked a randomized design, heterogeneities existed in age[11], Child score[4,11], the percentage of severe portal hypertension[4] and pretreatment with transarterial chemoembolization[11]. In the study by Akbulut *et al*[1], recurrence, overall survival and disease-free survival rates were comparable in the IBSA and non-IBSA groups, which were similar in age, gender, body mass index, underlying disease, donor type, graft-to-recipient weight ratio, Child-Pugh and model for end-stage liver disease scores, number of tumors, tumor size, alpha-fetoprotein level, Milan and University of California San Francisco (UCSF) criteria, tumor differentiation, macrovascular invasion, or median hospital stay.

Without results from prospective, randomized and controlled clinical trials in a large number of subjects, it is difficult at this stage to judge whether the use of IBSA during LT for HCC is more beneficial or not. However, the current available data may at least indicate that IBSA does not increase the risk of recurrence or metastasis.

What are the indications of IBSA?

Although the current studies partially reduced the fear of the theoretical risk of IBSA during cancer surgery, there are still a series of problems urgently requiring attention.

First, is it justified to take the risk of tumor dissemination during IBSA to avoid or reduce allogeneic blood transfusion? Allogeneic blood transfusion is not a cost-effective method as it is associated with increased risk of transfusion reactions and transfusion-transmitted infections, and induction of immunosuppression[27]. In hepatectomy for HCC, autologous blood transfusion has shown benefits in simulating liver synthetic function[28]. Moreover, allogeneic blood transfusion also increased the tumor recurrence rate by nearly 2-fold in a dose-dependent manner[28]. From the prevailing evidence, it was concluded that the correlation of cancer recurrence and allogeneic blood carried more weight than the theoretical risk of utilizing blood salvage in cancer surgery[28].

Second, do the remaining tumor cells after additional filtration by LDF still possess potential carcinogenicity? It is difficult to answer this question because of lacking of detailed and systemic studies, although the answer has been speculated by some authors[20,28]. Only 0.01%-0.000001% of circulating tumor cells have the potential to form metastatic lesions[20,25,28]. However, the effect of LDF in eliminating tumor cells is also limited[25]. In patients undergoing LT for HCC, a 10% remnant rate of tumor cells was reported by Liang *et al*[6]. However, another fact is that tumor cells ubiquitously exist in circulating blood of cancer patients[28]. Although the theoretical risk of the remnant tumor cells after reinfusion has not been verified[5,6], the correlation of circulating tumor cells and poor prognosis has been proved in various cancers[25,28]. In the study by Akbulut *et al*[1], more than 50% of patients were beyond the Milan and UCSF criteria in the IBSA group, but the metastasis rate in the IBSA group was similar to that in the non-IBSA group. Based on the above facts, it is difficult to distinguish whether the recurrence or metastasis is caused by the reinfusion or circulating tumor cells, but the risk indeed exists. There is the point of view that if tumor cells are already in circulation, is there any significance to adding a few more[20,28]?

Third, does IBSA always work well? Although the scavenging capacity of LDF is far beyond the amount of tumor cells remaining in the reinfusion blood[6,13], the remnant tumor cells appeared in all salvaged blood samples from the HCC patients with ruptured tumors[6]. Moreover, IBSA showed less benefit for patients with stage Ⅲ/Ⅳ HCC than for those with stage Ⅰ/Ⅱ HCC, when compared respectively with corresponding patients without IBSA[22]. The results warn against the application of IBSA in patients with more tumor cells in salvaged blood, such as patients with ruptured tumors or advanced HCC, which may exceed the filtering capacity of IBSA.

In conclusion, IBSA is a safe procedure of blood salvage in LT for HCC based on the available evidence to date. However, well-designed, randomized, controlled, prospective trials are urgently required to clarify the existing concerns.

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