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Intraoperative cell salvage with autologous transfusion in liver transplantation

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Abstract

Liver transplant (LT) is the primary treatment for patients with end-stage liver disease. About 25000 LTs are performed annually in the world. The potential for intraoperative bleeding is quite variable. However, massive bleeding is common and requires blood transfusion. Allogeneic blood transfusion has an immunosuppressive effect and an impact on recipient survival, in addition to the risk of transmission of viral infections and transfusion errors, among others. Techniques to prevent excessive bleeding or to use autologous blood have been proposed to minimize the negative effects of allogeneic blood transfusion. Intraoperative reinfusion of autologous blood is possible through previous self-donation or blood collected during the operation. However, LT does not normally allow autologous transfusion by prior self-donation. Hence, using autologous blood collected intraoperatively is the most feasible option. The use of intraoperative blood salvage autotransfusion (IBSA) minimizes the perioperative use of allogeneic blood, preventing negative transfusion effects without negatively impacting other clinical outcomes. The use of IBSA in patients with cancer is still a matter of debate due to the theoretical risk of reinfusion of tumor cells. However, studies have demonstrated the safety of IBSA in several surgical procedures, including LT for hepatocellular carcinoma. Considering the literature available to date, we can state that IBSA should be routinely used in LT, both in patients with cancer and in patients with benign diseases.

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Core tip: Intraoperative blood salvage autotransfusion is routinely used in liver transplant. In this article, we review its indications and contraindications, advantages and disadvantages, and cost-effectiveness.

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INTRODUCTION

Currently, about 14000 people are waiting for a liver transplant (LT) in the United States^[1]. The shortage of organs to meet the demand and the high complexity of the surgical procedure reinforce the need for constant technical improvement, aiming at the rational use of a limited source of grafts. Approximately 25000 LTs are performed annually worldwide^[2]. The surgical technique and equipment used vary among transplant centers.

LT has a highly variable intraoperative bleeding potential. Due to coagulopathy associated with chronic liver disease and surgical complexity, massive bleeding is common and may require blood transfusion^[3]. However, allogeneic blood transfusion causes immunosuppression^[4] and impacts clinical outcome^[5].

Autologous transfusion has been used as a strategy to decrease the incidence of the negative effects of allogeneic transfusion, avoiding the excessive use of donated blood, a limited resource. Autologous transfusion is performed with blood that has been collected from the same patient and stored or with blood collected intraoperatively. However, since there is no predetermined date for LT, except in cases involving living donors, collecting blood in advance from the recipient is usually not feasible. In this setting, intraoperative blood salvage autotransfusion (IBSA) is used as a strategy for autologous transfusion.

The aim of this review is to give an overview of the use of IBSA in LT and its role in the management of intraoperative bleeding associated with other measures. Indications and contraindications will be evaluated, as well as the advantages, disadvantages, and cost-effectiveness of using IBSA.

INTRAOPERATIVE BLEEDING MANAGEMENT

Managing blood loss is a fundamental part of LT. Even the transfusion of small volumes of blood can negatively impact the duration of hospitalization for the recipient. Transfusions above 6 units have an impact on survival and retransplantation rates^[6]. Although some authors question the real impact of transfusing small volumes of allogeneic blood on surgical outcomes, there is a consensus on the negative effects of massive transfusion^[6,7].

Fluid resuscitation with crystalloids and blood derivatives is not intended to restore the total volume of blood lost. An experimental study showed that rats subjected to hemorrhage and transfusion of an equal blood volume had a 20% increase in portal pressure and portal-collateral resistance compared with pre-bleeding pressure^[8]. The usual practice is the application of evidence-based concepts to maintain an adequate hemoglobin concentration, optimize hemostasis and minimize blood loss, which is called patient blood management^[9].

The use of thromboelastometry (TEM) to define the need for transfusion of coagulation factors is effective in reducing the need for blood transfusion^[7,9-11]. The use of TEM is superior to the use of standard massive transfusion protocols [transfusion of plasma, platelets, and packed red blood cells (PRBCs) in a 1:1:1 or 1:1:2 ratio]^[7]. However, the utilization of TEM has not shown any impact on mortality to date^[12].

HARMFUL EFFECTS OF ALLOGENEIC TRANSFUSION

Transfusion of blood components during LT is a predictive factor for postoperative mortality and tumor recurrence, by mechanisms not yet completely elucidated^[10]. In addition, it poses risks such as bacterial infections, anaphylaxis, hemolytic reactions, transfusion-related acute lung injury, and viral infections^[6]. Another negative effect of allogeneic transfusion, observed in kidney transplant recipients, is the potential for increased rates of acute cellular rejection due to alloimmunization to the antigens present in the transfused blood^[13,14]. In addition to the risks of blood transfusion, it should be noted that allogeneic blood has a lower oxygen-carrying capacity than autologous blood^[6,15].

Allogeneic transfusion is an independent risk factor for cancer-specific mortality and overall mortality in patients with cancer^[16,17]. The relationship between transfusion and survival is dose dependent, with a relative risk of 1.37 per unit of platelets and of 1.07 per unit of PRBCs^[18]. The need for blood transfusion is also a predictor of the need for renal replacement therapy. Patients undergoing LT who required more than 17.5 units of PRBCs or 3.5 units of platelets had an increased risk of postoperative dialysis^[19].

Allogeneic blood transfusion has an immunosuppressive effect^[4], caused not only by the allogeneic barrier but also by cellular damage that occurs due to the storage of red blood cells^[20]. Consequently, the rate of surgical wound infection is also influenced by allogeneic transfusion. A meta-analysis involving trauma patients showed an odds ratio of 3.45 (1.43-15.15) for a postoperative bacterial infection to occur after allogeneic blood transfusion^[21]. In another study, the need for more than 2 units of PRBCs also increased the risk of bacterial infection in LT recipients^[8]. The mechanism is not yet fully understood, but it is believed that both the immunosuppressive effect of transfusion and the supply of tumor growth factors present in the transfused blood are responsible for this effect^[22,23].

IBSA DEVICES

Reinfusion of blood collected in the surgical field is an ancient idea. It was first successfully used by John Duncan in 1885 during leg amputation^[24]. Almost a century later, in 1968, unwashed whole-blood autotransfusion was developed. This technique uses a simple and disposable device that allows reinfusion of blood. The initial results were encouraging^[25]. However, postoperative hemorrhage was frequently present, since the direct use of diluted blood serum led to an intense activation of the coagulation cascade and impaired hemostasis^[26].

Meanwhile, Brzica *et al*^[27] developed a system for intraoperative collection, washing, filtration, and concentration of blood. The collected blood was mixed with an anticoagulant solution and then reinfused into the patient^[27]. Current IBSA devices aspirate blood collected in the operative field through a dual-lumen suction catheter, add citrate as an anticoagulant, and then centrifuge the blood to separate its components. The autotransfusion solution is called acid-citrate-dextrose anticoagulant.

Approximately 70% of the blood collected can be reinfused^[6]. A crucial step is the clearance of free hemoglobin from the reinfused blood, because this molecule can promote pulmonary, renal, and platelet dysfunction^[28]. The red blood cells are then resuspended in saline to a hematocrit of 50%-70%, thus being ready for reinfusion. Each 200 mL of red blood cell concentrate recovered in this way is equivalent to 1 unit of PRBCs^[10]. The addition of leukocyte depletion filters (LDFs) to IBSA devices reduces the number of malignant cells in the reinfused blood^[10]. Since blood recovered by IBSA does not contain coagulation factors, TEM should be used to assess the efficiency of blood coagulation and the need for hemostasis management^[12]. In addition to reducing platelet dysfunction, the processing of blood collected intraoperatively with IBSA reduces the systemic inflammatory response and balances the pro and anti-inflammatory cytokines present in the blood to be reinfused, as compared with direct reinfusion of blood^[26]. Two devices are most commonly used for IBSA in surgery, Cell SaverTM and HemoSepTM. However, so far, only a few studies have compared their efficiency and costs^[29].

IBSA TO AVOID ALLOGENEIC TRANSFUSION

LT is responsible for about 25% of the total hospital consumption of blood products^[7]. Efforts should therefore be made to avoid unnecessary transfusions^[29]. Although the

refinement of surgical techniques has reduced the need for blood transfusion in LT, strategies that aim to minimize such a need should be promoted.

The use of IBSA may reduce the need for allogeneic blood transfusion (level of evidence IA)^[9,30-32]. Evidence shows that the use of IBSA prevents the use of 1.1 ± 1.7 units of PRBCs^[31,32]. A recent study showed that, in 150 consecutive LT patients, the use of IBSA could reduce the need for blood transfusion in up to 2 units of PRBCs^[33]. A recent meta-analysis estimated a 23% absolute risk reduction in receiving allogeneic transfusion with the utilization of IBSA^[34].

ADVANTAGES OF IBSA

Reducing the need for allogeneic transfusion may lead to a decrease in treatment costs. In addition, blood for transfusion is a scarce resource. North American studies estimated the cost of 2 units of PRBCs to be ranging from US\$515.00 to US\$1303.68^[35-37]. A more recent study estimated the cost of 2 units of red blood cells to be between US\$1270.49 and US\$2458.77 and hypothesized that older estimates may have underestimated transfusion costs^[38]. A review of 6 European studies estimated the cost of transfusion of 2 units of PRBCs to be around €877.69^[39]. Furthermore, the use of IBSA has shown to become cost-effective when bleeding exceeds 614 mL^[40]. Other studies have also shown that IBSA systems are cost-effective even for small volumes of blood loss^[41,42]. A prospective study of 660 LT patients estimated that, as compared to LT using only allogeneic transfusion, the use of IBSA has provided total cost savings of US\$188618.00 over a 5-year study period^[43].

The use of IBSA may reduce the rate of surgical infection by avoiding the immunosuppressive effect of allogeneic transfusion^[7]. The duration of hospital stay is also reduced, thus decreasing treatment-related costs^[30]. In addition, the use of IBSA may be an alternative for patients who refuse allogeneic blood for religious reasons, such as Jehovah's Witnesses. However, no consensus has been reached on the use of IBSA in LT^[7]. Some studies have not identified the above-mentioned potential advantages^[6,31,44], and cost-effectiveness has also been questioned^[7].

DISADVANTAGES OF IBSA

Some risks and disadvantages of using IBSA in LT have been noted. There is a risk of acute kidney injury secondary to hemolysis. However, this is a rare complication described in a few case reports^[7,44]. Another unusual adverse effect of IBSA is salvaged blood syndrome. It is triggered by the activation of the coagulation cascade, leading to increased vascular permeability, acute renal failure, and lung injury. These events, although severe, are extremely rare. In a review of 36000 cases using IBSA, only 18 (0.05%) cases of disseminated intravascular coagulation were diagnosed, but not all of them could be considered salvaged blood syndrome^[44]. Despite the theoretical risk that the use of IBSA may cause disseminated intravascular coagulation due to reinfusion of free hemoglobin, denatured proteins, and microaggregates of platelets and leukocytes, studies have failed to demonstrate a significant increase in the incidence of this complication^[9].

The risk of infusing bacteria present in the operative field is biologically plausible, since the collected blood may be contaminated by bacteria from the patient's skin or from the bile duct, with the possibility of cholangitis. However, a recent study failed to demonstrate an increase in the frequency of positive blood cultures when IBSA was used to recover contaminated blood^[45]. Some authors support the precaution of avoiding the use of IBSA when bile is present in the operative field^[7].

With regard to the costs associated with the use of IBSA, an alternative is to place the device in standby mode during LT, to be used only in cases where there is a significant blood loss^[9,20]. In this case, only a dual-lumen suction catheter, an anticoagulant solution, and a sterile container are employed.

Sickle cell anemia is a relative contraindication to IBSA utilization^[46]. The presence of sickle cell trait, in turn, is still a matter of debate. A case series suggested that IBSA is a safe practice in this group of patients^[46].

Despite the existence of undesirable effects, these are rare and the use of IBSA has a good safety profile. A multicenter study involving more than 33000 patients estimated the rate of adverse effects associated with the use of IBSA to be between 0% and 0.006%^[47].

USE OF IBSA IN ONCOLOGICAL PATIENTS

The potential risk of infusing malignant cells into patients operated on for cancer is the main concern about the safety of IBSA. Oncological surgery is still considered a relative contraindication to IBSA^[7]. The presence of neoplastic cells in blood samples from an autotransfusion system was first identified in 1975^[48]. Since then, several reports of neoplastic cells found in blood samples collected by IBSA have contributed to increase mistrust regarding the safety of using these devices in patients with cancer^[48].

Large amounts of circulating neoplastic cells are found in patients with cancer^[48]. The amount of neoplastic cells found in the bloodstream has been shown to be inversely correlated with patient survival^[48]. However, there is no confirmation of the viability of these cells or of their potential to produce metastases^[48], since the presence of neoplastic cells in the circulation cannot *per se* imply the development of metastases. Animal studies have demonstrated that tumor development due to the implantation of neoplastic cells present in the bloodstream is a rare event^[48]. Although there is a great deal of evidence based on *in vitro* studies and surrogate endpoints, the only clinical evidence linking the use of IBSA to the development of metastasis comes from a case reported in 1975^[49].

Contrary to studies that raise concerns about the safety of IBSA in patients with cancer, a meta-analysis^[49] demonstrated the safety of using IBSA, also suggesting that the use of IBSA may be a protective factor against cancer recurrence, with an odds ratio of 0.65 (0.43-0.98). It is interesting to note that, in the subgroup analysis of the studies comparing IBSA with preoperative autologous donation (PAD), there was still a slight advantage in favor of the IBSA group. These data contradict the statement that the advantages of IBSA only appear when compared with the use of allogeneic blood. Since the blood used in PAD does not have the disadvantages of allogeneic transfusion, demonstrating the non-inferiority of IBSA in relation to PAD enhances the safety of these devices. Although this result comes from a study in which different types neoplasms in different organs and systems were evaluated, the large number of patients allocated ($n = 2326$) increases the significance of the data. In addition, 1 of the 10 studies included in the meta-analysis involved patients with hepatocellular carcinoma^[49].

To date, 4 studies have evaluated the oncological safety of using IBSA in LT. One of these studies used LDFs and evaluated the presence of malignant cells in the aspirate by *in vitro* evaluation with polymerase chain reaction, concluding that the device is effective in removing malignant cells from the aspirate, except in cases of tumor rupture^[50]. The other 3 available studies evaluated clinical outcomes, such as mortality and recurrence. None of them demonstrated negative effects associated with the use of IBSA. However, all of them suggested that additional studies are warranted to confirm or refute this hypothesis^[51-53].

The addition of LDFs to IBSA was implemented in the 1990s to increase the safety of the procedure. These filters eliminate all identifiable neoplastic cells from blood obtained intraoperatively, unlike the standard IBSA devices^[54]. The efficacy of LDFs in removing tumor cells has been demonstrated in *in vitro* and *in vivo* studies, being considered safe in patients with non-ruptured hepatocellular carcinoma during LT^[7]. The irradiation of blood prior to its reinfusion has also been proposed^[20]. Blood irradiation ensures a 10 to 12 log reduction in the number of infused tumor cells, which is considered sufficient to eliminate all tumor cells without impairing the function of red blood cells^[20]. Besides that, irradiation also damages the DNA of malignant cells, reducing their multiplication capacity.

A meta-analysis evaluating the safety of IBSA in patients with cancer suggested that both the use of LDFs and the irradiation of blood to be reinfused are unnecessary to ensure the safety of the procedure, since these methods were not used in the evaluated studies and even though oncological safety was obtained^[49]. Moreover, the use of an RC-400 filter adds on average US\$30 to every 2 units of PRBCs obtained^[54], generating an unnecessary cost. In the light of the literature available to date, the European Society of Anesthesiology does not contraindicate the use of IBSA in patients with cancer^[55].

CONCLUSION

The use of IBSA is indicated in LT because the possibility of bleeding exceeding 20% of total blood volume is anticipated^[46], being considered safe and cost-effective. Although the use of IBSA should be encouraged, concerns remain about the safety of IBSA in specific scenarios, such as the treatment of liver tumors with intraperitoneal

rupture^[56] and in patients with sickle cell anemia.

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