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# Intraoperative cell salvage with autologous transfusion in liver transplantation

Pinto MA *et al.* Intraoperative cell salvage with autologous transfusion in LT

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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.

**Key words**: Liver transplantation; Cell saver; Hepatocellular carcinoma; Blood transfusion; Cell salvage

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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[5]. 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 Saver™ and HemoSep™. 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$188 618.00 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.

# REFERENCES

1 **Scientific Registry of Transplant Recipients**. Data - OPTN [Internet]. Available from: URL: https://optn.transplant.hrsa.gov/data/

2 **Shukla A**, Vadeyar H, Rela M, Shah S. Liver Transplantation: East versus West. *J Clin Exp Hepatol* 2013; **3**: 243-253 [PMID: 25755506 DOI: 10.1016/j.jceh.2013.08.004]

3 **Chidananda Swamy M**. Blood transfusion practices in liver transplantation. *Indian J Anaesth* 2014; **58**: 647-651 [PMID: 25535430 DOI: 10.4103/0019-5049.144677]

4 **Landers DF**, Hill GE, Wong KC, Fox IJ. Blood transfusion-induced immunomodulation. *Anesth Analg* 1996; **82**: 187-204 [PMID: 8712400 DOI: 10.1213/00000539-199601000-00035]

5 **Ramos E**, Dalmau A, Sabate A, Lama C, Llado L, Figueras J, Jaurrieta E. Intraoperative red blood cell transfusion in liver transplantation: influence on patient outcome, prediction of requirements, and measures to reduce them. *Liver Transpl* 2003; **9**: 1320-1327 [PMID: 14625833 DOI: 10.1016/jlts.2003.50204]

6 **Duramaz A**, Bilgili MG, Bayram B, Ziroğlu N, Edipoğlu E, Öneş HN, Kural C, Avkan MC. The role of intraoperative cell salvage system on blood management in major orthopedic surgeries: a cost-benefit analysis. *Eur J Orthop Surg Traumatol* 2018; **28**: 991-997 [PMID: 29214459 DOI: 10.1007/s00590-017-2098-2]

7 **Cleland S**, Corredor C, Ye JJ, Srinivas C, McCluskey SA. Massive haemorrhage in liver transplantation: Consequences, prediction and management. *World J Transplant* 2016; **6**: 291-305 [PMID: 27358774 DOI: 10.5500/wjt.v6.i2.291]

8 **Kravetz D**, Sikuler E, Groszmann RJ. Splanchnic and systemic hemodynamics in portal hypertensive rats during hemorrhage and blood volume restitution. *Gastroenterology* 1986; **90**: 1232-1240 [PMID: 3956942 DOI: 10.1055/s-2007-1013006]

9 **Clevenger B**, Mallett SV, Klein AA, Richards T. Patient blood management to reduce surgical risk. *Br J Surg* 2015; **102**: 1325-1337; discussion 1324 [PMID: 26313653 DOI: 10.1002/bjs.9898]

10 **Clevenger B**, Mallett SV. Transfusion and coagulation management in liver transplantation. *World J Gastroenterol* 2014; **20**: 6146-6158 [PMID: 24876736 DOI: 10.3748/wjg.v20.i20.6146]

11 **Gurusamy KS**, Pissanou T, Pikhart H, Vaughan J, Burroughs AK, Davidson BR. Methods to decrease blood loss and transfusion requirements for liver transplantation. *Cochrane Database Syst Rev* 2011; **(12)**: CD009052 [PMID: 22161443 DOI: 10.1002/14651858.CD009052.pub2]

12 **Afshari A**, Wikkelsø A, Brok J, Møller AM, Wetterslev J. Thrombelastography (TEG) or thromboelastometry (ROTEM) to monitor haemotherapy versus usual care in patients with massive transfusion. *Cochrane Database Syst Rev* 2011; **(3)**: CD007871 [PMID: 21412912 DOI: 10.1002/14651858.CD007871.pub2]

13 **Holt S**, Donaldson H, Hazlehurst G, Varghese Z, Contreras M, Kingdon E, Sweny P, Burns A. Acute transplant rejection induced by blood transfusion reaction to the Kidd blood group system. *Nephrol Dial Transplant* 2004; **19**: 2403-2406 [PMID: 15299103 DOI: 10.1093/ndt/gfh333]

14 **Lenhard V**, Hansen B, Roelcke D, Dreikorn K, Wernet P, Bockhorn H, Fassbinder W, Fetta RF, Wilms H, Gumbel B, Albert FW, Ewald RW, Sprenger-Klasen I, Goldmann SF. Influence of Lewis and other blood group systems in kidney transplantation. *Proc Eur Dial Transplant Assoc* 1983; **19**: 432-437 [PMID: 6348744]

15 **Linder BJ**, Thompson RH, Leibovich BC, Cheville JC, Lohse CM, Gastineau DA, Boorjian SA. The impact of perioperative blood transfusion on survival after nephrectomy for non-metastatic renal cell carcinoma (RCC). *BJU Int* 2014; **114**: 368-374 [PMID: 24471825 DOI: 10.1111/bju.12535]

16 **Soubra A**, Zabell JR, Adejoro O, Konety BR. Effect of perioperative blood transfusion on mortality for major urologic malignancies. *Clin Genitourin Cancer* 2015; **13**: e173-e181 [PMID: 25600760 DOI: 10.1016/j.clgc.2014.12.006]

17 **Linder BJ**, Frank I, Cheville JC, Tollefson MK, Thompson RH, Tarrell RF, Thapa P, Boorjian SA. The impact of perioperative blood transfusion on cancer recurrence and survival following radical cystectomy. *Eur Urol* 2013; **63**: 839-845 [PMID: 23332883 DOI: 10.1016/j.eururo.2013.01.004]

18 **de Boer MT**, Christensen MC, Asmussen M, van der Hilst CS, Hendriks HG, Slooff MJ, Porte RJ. The impact of intraoperative transfusion of platelets and red blood cells on survival after liver transplantation. *Anesth Analg* 2008; **106**: 32-44, table of contents [PMID: 18165548 DOI: 10.1213/01.ane.0000289638.26666.ed]

19 **Reichert B**, Kaltenborn A, Becker T, Schiffer M, Klempnauer J, Schrem H. Massive blood transfusion after the first cut in liver transplantation predicts renal outcome and survival. *Langenbecks Arch Surg* 2014; **399**: 429-440 [PMID: 24682384 DOI: 10.1007/s00423-014-1181-y]

20 **Hansen E**, Bechmann V, Altmeppen J. Intraoperative blood salvage in cancer surgery: safe and effective? *Transfus Apher Sci* 2002; **27**: 153-157 [PMID: 12350050 DOI: 10.1016/S1473-0502(02)00037-X]

21 **Hill GE**, Frawley WH, Griffith KE, Forestner JE, Minei JP. Allogeneic blood transfusion increases the risk of postoperative bacterial infection: a meta-analysis. *J Trauma* 2003; **54**: 908-914 [PMID: 12777903 DOI: 10.1097/01.TA.0000022460.21283.53]

22 **Upile T**, Jerjes W, Mahil J, Sudhoff H, Hopper C, Wright A. Blood product transfusion and cancer prognosis. *Clin Adv Hematol Oncol* 2009; **7**: 656-661 [PMID: 20040905 DOI: 10.4000/cybergeo.26756]

23 **Vamvakas EC**, Blajchman MA. Transfusion-related immunomodulation (TRIM): an update. *Blood Rev* 2007; **21**: 327-348 [PMID: 17804128 DOI: 10.1016/j.blre.2007.07.003]

24 **Duncan J**. On Re-Infusion of Blood in Primary and Other Amputations. *Br Med J* 1886; **1**: 192-193 [PMID: 20751443 DOI: 10.1136/bmj.1.1309.192]

25 **Klebanoff G**, Watkins D. A disposable autotransfusion unit. *Am J Surg* 1968; **116**: 475-476 [PMID: 5675925 DOI: 10.1016/0002-9610(68)90250-X]

26 **Gäbel J**, Malm CJ, Radulovic V, Shams Hakimi C, Westerberg M, Jeppsson A. Cell saver processing mitigates the negative effects of wound blood on platelet function. *Acta Anaesthesiol Scand* 2016; **60**: 901-909 [PMID: 27137133 DOI: 10.1111/aas.12730]

27 **Brzica SM Jr**, Pineda AA, Taswell HF. Autologous blood transfusion. *CRC Crit Rev Clin Lab Sci* 1978; **10**: 31-56 [PMID: 752444]

28 **Garg P**, Malhotra A, Desai M, Sharma P, Bishnoi AK, Tripathi P, Rodricks D, Pandya H. Pretransfusion Comparison of Dialyser-Based Hemoconcentrator With Cell Saver System for Perioperative Cell Salvage. *Innovations* (Phila) 2015; **10**: 334-341 [PMID: 26418303 DOI: 10.1097/IMI.0000000000000180]

29 **Gunaydin S**, Robertson C, Budak AB, Gourlay T. Comparative evaluation of blood salvage techniques in patients undergoing cardiac surgery with cardiopulmonary bypass. *Perfusion* 2018; **33**: 105-109 [PMID: 28856967 DOI: 10.1177/0267659117728328]

30 **Elmalky M**, Yasin N, Rodrigues-Pinto R, Stephenson J, Carroll C, Smurthwaite G, Verma R, Mohammad S, Siddique I. The safety, efficacy, and cost-effectiveness of intraoperative cell salvage in metastatic spine tumor surgery. *Spine J* 2017; **17**: 977-982 [PMID: 28323241 DOI: 10.1016/j.spinee.2017.03.004]

31 **Al-Mandhari S**, Maddali MM, Al-Bahrani MJ. Cell salvage during coronary artery bypass surgery and allogenic blood exposure. *Asian Cardiovasc Thorac Ann* 2015; **23**: 913-916 [PMID: 26113735 DOI: 10.1177/0218492315592788]

32 **Wang G**, Bainbridge D, Martin J, Cheng D. The efficacy of an intraoperative cell saver during cardiac surgery: a meta-analysis of randomized trials. *Anesth Analg* 2009; **109**: 320-330 [PMID: 19608798 DOI: 10.1213/ane.0b013e3181aa084c]

33 **Massicotte L**, Thibeault L, Beaulieu D, Roy JD, Roy A. Evaluation of cell salvage autotransfusion utility during liver transplantation. *HPB* (Oxford) 2007; **9**: 52-57 [PMID: 18333113 DOI: 10.1080/13651820601090596]

34 **The Cochrane Collaboration**, editor. Cell salvage for minimising perioperative allogeneic blood transfusion. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley amd Sons, Ltd, 1996: 475

35 **Cantor SB**, Hudson DV Jr, Lichtiger B, Rubenstein EB. Costs of blood transfusion: a process-flow analysis. *J Clin Oncol* 1998; **16**: 2364-2370 [PMID: 9667252 DOI: 10.1200/JCO.1998.16.7.2364]

36 **Forbes JM**, Anderson MD, Anderson GF, Bleecker GC, Rossi EC, Moss GS. Blood transfusion costs: a multicenter study. *Transfusion* 1991; **31**: 318-323 [PMID: 2020994 DOI: 10.1046/j.1537-2995.1991.31491213295.x]

37 **Crémieux PY**, Barrett B, Anderson K, Slavin MB. Cost of outpatient blood transfusion in cancer patients. *J Clin Oncol* 2000; **18**: 2755-2761 [PMID: 10894876 DOI: 10.1200/JCO.2000.18.14.2755]

38 **Shander A**, Hofmann A, Ozawa S, Theusinger OM, Gombotz H, Spahn DR. Activity-based costs of blood transfusions in surgical patients at four hospitals. *Transfusion* 2010; **50**: 753-765 [PMID: 20003061 DOI: 10.1111/j.1537-2995.2009.02518.x]

39 **Abraham I**, Sun D. The cost of blood transfusion in Western Europe as estimated from six studies. *Transfusion* 2012; **52**: 1983-1988 [PMID: 22313531 DOI: 10.1111/j.1537-2995.2011.03532.x]

40 **Gum JL**, Carreon LY, Kelly MP, Hostin R, Robinson C, Burton DC, Polly DW, Shaffrey CI, LaFage V, Schwab FJ, Ames CP, Kim HJ, Smith JS, Bess RS; International Spine Study Group. Cell Saver for Adult Spinal Deformity Surgery Reduces Cost. *Spine Deform* 2017; **5**: 272-276 [PMID: 28622903 DOI: 10.1016/j.jspd.2017.01.005]

41 **Kelly PD**, Parker SL, Mendenhall SK, Bible JE, Sivasubramaniam P, Shau DN, McGirt MJ, Devin CJ. Cost-effectiveness of cell saver in short-segment lumbar laminectomy and fusion (≤3 levels). *Spine* (Phila Pa 1976) 2015; **40**: E978-E985 [PMID: 25929204 DOI: 10.1097/BRS.0000000000000955]

42 **Chanda A**, Smith DR, Nanda A. Autotransfusion by cell saver technique in surgery of lumbar and thoracic spinal fusion with instrumentation. *J Neurosurg* 2002; **96**: 298-303 [PMID: 11990838 DOI: 10.3171/spi.2002.96.3.0298]

43 **Phillips SD**, Maguire D, Deshpande R, Muiesan P, Bowles MJ, Rela M, Heaton ND. A prospective study investigating the cost effectiveness of intraoperative blood salvage during liver transplantation. *Transplantation* 2006; **81**: 536-540 [PMID: 16495800 DOI: 10.1097/01.tp.0000199318.17013.c5]

44 **Minkara AA**, Lin AY, Vitale MG, Roye DP Jr. Acute Kidney Injury Secondary to Cell Saver in Posterior Spinal Fusion. *Spine Deform* 2017; **5**: 430-434 [PMID: 29050721 DOI: 10.1016/j.jspd.2017.03.010]

45 **Feltracco P**, Michieletto E, Barbieri S, Serra E, Rizzi S, Salvaterra F, Cillo U, Ori C. Microbiologic contamination of intraoperative blood salvaged during liver transplantation. *Transplant Proc* 2007; **39**: 1889-1891 [PMID: 17692644 DOI: 10.1016/j.transproceed.2007.05.005]

46 **You D**, Peiro-Garcia A, Ferri-de-Barros F, Parsons D. Hemolysis Following Intraoperative Cell Salvage Replacement in a Scoliosis Patient With Sickle Cell Trait: A Case Report. *Spine* (Phila Pa 1976) 2017; **42**: E1331-E1333 [PMID: 28441316 DOI: 10.1097/BRS.0000000000002211]

47 **DeAndrade D**, Waters JH, Triulzi DJ, Alarcon L, Wisniewski MK, Dyga R, Yazer MH. Very low rate of patient-related adverse events associated with the use of intraoperative cell salvage. *Transfusion* 2016; **56**: 2768-2772 [PMID: 27614051 DOI: 10.1111/trf.13791]

48 **Lyon TD**, Ferroni MC, Turner RM 2nd, Jones C, Jacobs BL, Davies BJ. Short-term Outcomes of Intraoperative Cell Saver Transfusion During Open Partial Nephrectomy. *Urology* 2015; **86**: 1153-1158 [PMID: 26387849 DOI: 10.1016/j.urology.2015.09.008]

49 **Waters JH**, Yazer M, Chen YF, Kloke J. Blood salvage and cancer surgery: a meta-analysis of available studies. *Transfusion* 2012; **52**: 2167-2173 [PMID: 22321196 DOI: 10.1111/j.1537-2995.2011.03555.x]

50 **Liang TB**, Li DL, Liang L, Li JJ, Bai XL, Yu W, Wang WL, Shen Y, Zhang M, Zheng SS. Intraoperative blood salvage during liver transplantation in patients with hepatocellular carcinoma: efficiency of leukocyte depletion filters in the removal of tumor cells. *Transplantation* 2008; **85**: 863-869 [PMID: 18360269 DOI: 10.1097/TP.0b013e3181671f2e]

51 **Araujo RL**, Pantanali CA, Haddad L, Rocha Filho JA, D'Albuquerque LA, Andraus W. Does autologous blood transfusion during liver transplantation for hepatocellular carcinoma increase risk of recurrence? *World J Gastrointest Surg* 2016; **8**: 161-168 [PMID: 26981190 DOI: 10.4240/wjgs.v8.i2.161]

52 **Foltys D**, Zimmermann T, Heise M, Kaths M, Lautem A, Wisser G, Weiler N, Hoppe-Lotichius M, Hansen T, Otto G. Liver transplantation for hepatocellular carcinoma--is there a risk of recurrence caused by intraoperative blood salvage autotransfusion? *Eur Surg Res* 2011; **47**: 182-187 [PMID: 21986299 DOI: 10.1159/000330746]

53 **Muscari F**, Suc B, Vigouroux D, Duffas JP, Migueres I, Mathieu A, Lavayssiere L, Rostaing L, Fourtanier G. Blood salvage autotransfusion during transplantation for hepatocarcinoma: does it increase the risk of neoplastic recurrence? *Transpl Int* 2005; **18**: 1236-1239 [PMID: 16221153 DOI: 10.1111/j.1432-2277.2005.00207.x]

54 **Edelman MJ**, Potter P, Mahaffey KG, Frink R, Leidich RB. The potential for reintroduction of tumor cells during intraoperative blood salvage: reduction of risk with use of the RC-400 leukocyte depletion filter. *Urology* 1996; **47**: 179-181 [PMID: 8607229 DOI: 10.1016/S0090-4295(99)80411-7]

55 **Kozek-Langenecker SA**, Ahmed AB, Afshari A, Albaladejo P, Aldecoa C, Barauskas G, De Robertis E, Faraoni D, Filipescu DC, Fries D, Haas T, Jacob M, Lancé MD, Pitarch JVL, Mallett S, Meier J, Molnar ZL, Rahe-Meyer N, Samama CM, Stensballe J, Van der Linden PJF, Wikkelsø AJ, Wouters P, Wyffels P, Zacharowski K. Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology: First update 2016. *Eur J Anaesthesiol* 2017; **34**: 332-395 [PMID: 28459785 DOI: 10.1097/EJA.0000000000000630]

56 **Chedid AD**, Klein PW, Tiburi MF, Villwock MM, Bassani LE, Chedid MF. Spontaneous rupture of hepatocellular carcinoma with haemoperitoneum: a rare condition in Western countries. *HPB* (Oxford) 2001; **3**: 227-230 [PMID: 18333020 DOI: 10.1080/136518201753242262]

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