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REVIEW ARTICLE

Red blood cell transfusion in liver resection

Nicholas Latchana [1,2] · Dhruvin H. Hirpara [1,2] · Julie Hallet [1,2] · Paul J. Karanicolas [1,2,3]

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Abstract

Background Several modalities exist for the management of hepatic neoplasms. Resection, the most effective approach, carries significant risk of hemorrhage. Blood loss may be corrected with red blood cell transfusion (RBCT) in the short term, but may ultimately contribute to negative outcomes.

Purpose Using available literature, we seek to define the frequency and risk factors of blood loss and transfusion following hepatectomy. The impact of blood loss and RBCT on short- and long-term outcomes is explored with an emphasis on peri-operative methods to reduce hemorrhage and transfusion.

Results Following hepatic surgery, 25.2–56.8% of patients receive RBCT. Patients who receive RBCT are at increased risk of surgical morbidity in a dose-dependent manner. The relationship between blood transfusion and surgical mortality is less apparent. RBCT might also impact long-term oncologic outcomes including disease recurrence and overall survival. Risk factors for bleeding and blood transfusion include hemoglobin concentration < 12.5 g/dL, thrombocytopenia, pre-operative biliary drainage, presence of background liver disease (such as cirrhosis), coronary artery disease, male gender, tumor characteristics (type, size, location, presence of vascular involvement), extent of hepatectomy, concomitant extrahepatic organ resection, and operative time. Strategies to mitigate blood loss or transfusion include pre-operative (iron, erythropoietin), intra-operative (vascular occlusion, parenchymal transection techniques, hemostatic agents, antifibrinolytics, low central pressure, hemodilution, autologous blood recycling), and post-operative (normothermia, correction of coagulopathy, optimization of nutrition, restrictive transfusion strategy) methods.

Conclusion Blood loss during hepatectomy is common and several risk factors can be identified pre-operatively. Blood loss and RBCT during hepatectomy is associated with post-operative morbidity and mortality. Disease-free recurrence, disease-specific survival, and overall survival may be associated with blood loss and RBCT during hepatectomy. Attention to pre-operative, intra-operative, and post-operative strategies to reduce blood loss and RBCT is necessary.

Keywords Liver · Cancer · Hemorrhage · Transfusion

Introduction

Surgical resection and transplantation are the mainstay of curative approaches for primary and secondary hepatic tumors. Transplantation is limited by the availability of suitable grafts, requires immunosuppression, and is therefore used in a limited variety of hepatic neoplasms. Given these limitations, hepatic resection is more widespread. Liver resection is most commonly performed for hepatic metastases, thus resection rates are higher in regions with an increased incidence of primary colorectal cancer [1]. Hepatocellular carcinoma and cholangiocarcinoma are the most common primary malignant tumors of the liver while hepatic adenoma is the most the common benign neoplasm to undergo resection [2]. Rarely, liver resection is performed for hepatolithiasis, angiomyolipoma, hemangioma, focal nodular hyperplasia, and bile duct strictures [2].

Thirty-day mortality following partial hepatectomy is 1.9% and increases to 5.8% for extended hepatectomy, whereas morbidity has been reported between 22.6 and 32.8% [3]. Bleeding represents a major source of morbidity following surgery and is often managed with red blood transfusion

✉ Paul J. Karanicolas
paul.karanicolas@sunnybrook.ca

1 Department of Surgery, University of Toronto, Toronto, Ontario, Canada

2 Division of General Surgery, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada

3 Department of Surgery, Sunnybrook Health Sciences Centre, 2075 Bayview Avenue, Toronto, Ontario M4N 3M5, Canada

(RBCT). Unarguably, RBCT is necessary in some clinical situations to improve tissue perfusion and oxygenation. However, RBCT is not without consequence as it may result in acute lung injury and worse 30-day morbidity and mortality [4, 5]. It has also been associated with worse long-term outcomes such as increased tumor recurrence potentially secondary to immunosuppressive effects [6]. Thereby, efforts to minimize blood transfusions have been carried out [5]. Several randomized trials have demonstrated that restrictive blood transfusion strategies (transfusion for hemoglobin < 7.0–8.0 g/dL) yield non-inferior results to liberal transfusion strategies [7, 8]. Furthermore, restrictive strategies can result in economic savings of $760 USD for each unit of blood that is not transfused [9]. As a result, many centers have adopted a restrictive transfusion protocol to minimize the untoward effects of unnecessary blood transfusion and its associated costs.

Bleeding during hepatectomy is commonly encountered and the subsequent impact of RBCT on outcomes is an important concern. Yet, few studies have summarized the impact of bleeding and RBCT on short- and long-term outcomes after hepatectomy together with an in-depth analysis of recommended practices to reduce unnecessary RBCT. Herein, we highlight available literature focusing on the scope of the problem, short- and long-term implications, risk factors, and strategies to mitigate blood loss and RBCT associated with hepatic resection.

Blood loss and transfusion in hepatectomy

Frequency

Intra-operative blood loss is highly correlated with RBCT, but much harder to measure reliably and thus prone to inaccuracy. Therefore, RBCT is a better measure of extent of bleeding, and will be the focus through the remainder of this manuscript. Within the literature, there is great variation in the proportion of patients who receive RBCT following hepatectomy(25.2%–56.8%) [10–12]. For example, one analysis of the National Inpatient Sample (NIS) in the USA revealed 56.8% of patients received a blood transfusion, while in an analysis of the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) the transfusion rate was half that [11, 12]. These variations are likely related to differences in the timeframe of the studies, and perhaps due to differences in the types of patients included. The NIS evaluation was carried out between 1998 and 2004, whereas the NSQIP study sampled patients between 2007 and 2012. Over the corresponding timeframe, there was a trend towards increased use of parenchyma-sparing resection techniques, decrease in the quantity of liver segments resected, and several other changes in practice patterns [13]. Other studies confirm this trend [10].

Heterogeneity between the large databases may also account for some of differences. NSQIP includes a select group of hospitals in the USA (US) committed to quality improvement initiatives, whereas, NIS includes all US hospitals. Differences across the same procedure have been previously reported [14]. It is plausible that those hospitals participating in NSQIP have lower RBCT rate due systematic examination of surgical outcomes and initiation of quality improvement processes [14]. Nonetheless, these studies provide insight into the nature of the problem.

Short-term outcomes

RBCT can impact several short-term outcomes following hepatectomy. Immunomodulatory effects of RBCT on the recipient and the resultant susceptibility to infection and impaired anti-tumor activity are key mechanisms that may impact patient outcomes [15]. Furthermore, RBCT may initiate pro-inflammatory mediators that can lead to multi-organ failure and mortality [15].

Surgical morbidity after hepatectomy increases with the use of RBCT. Several retrospective studies have compared RBCT in hepatectomy with a reported complication rate of 17–64% among those who receive transfusion compared with 5–33% without a transfusion [12, 16–19]. The difference in the reported rate between studies varies widely and this can be partially attributed to the differing definitions of morbidity between studies and heterogenous study groups. Post-operative infection is the most common morbidity encountered; further reinforcing the immunomodulatory theory regarding mechanistic action.

RBCT is associated with a higher rate of mortality in some studies. For example, in one study, 30-day post-operative mortality was reported as 5.6% in patients who received RBCT after hepatectomy compared to 1.0% in patients without a blood transfusion [12]. This trend is not seen in several other studies however, possibly due to limited power to appropriately investigate this effect [10]. Nevertheless, the strong association with post-operative morbidity, potential association with mortality, and the reality that RBCT is a limited resource makes a compelling case to avoid RBCT when possible.

Oncologic outcomes

Blood loss and transfusion after hepatectomy may also increase risk of cancer recurrence, thereby decreasing disease-specific survival and overall survival (OS) [20]. This is likely multifactorial, related to suboptimal resection, post-operative complications, and possibly the immunomodulatory and pro-inflammatory effects of RBCT [15]. A single institution review of long-term outcomes for patients undergoing resection of colorectal liver metastasis revealed 5-year OS was worse in patients who received a RBCT compared to those that did not receive a transfusion after controlling for other potential

confounders (45.9 vs. 61.0%, respectively; $p < 0.0001$) [21]. Five-year recurrence-free survival (RFS) was also lower in patients who received a blood transfusion compared to those who did not (15.5 vs. 31.6%, respectively; $p < 0.0001$) [21]. In a systematic review involving 18 studies, 10 studies demonstrated an association between transfusion and OS [10]. Thus, bleeding and blood transfusion may impact oncologic outcomes but the relationship and mechanism remain uncertain.

Risk factors

Several studies have investigated risk factors associated with RBCT after hepatectomy (Table 1) [20, 22–25]. Pre-operative risk factors most consistently associated with blood loss include hemoglobin concentration < 12.5 g/dL, thrombocytopenia, pre-operative biliary drainage, presence of background liver disease (such as cirrhosis), coronary artery disease, and male gender [20, 26]. Intra-operative factors associated with increased bleeding include tumor characteristics (type, size, location, presence of vascular involvement), extent of hepatectomy, concomitant extrahepatic organ resection, and operative time [20, 26]. Some of the pre-operative risk factors may be modifiable such as anemia and pre-operative biliary drainage. Overall, surgeons should be aware of these factors and take them into consideration to assess risk and direct mitigation strategies.

Risk calculators

In light of the identified risk factors above, several groups have designed tools to predict the risk for blood transfusion [26–28]. Recently, a simplified tool that incorporates features common to several of the calculators was developed to include primary liver malignancy, major liver resection, and hemoglobin ≤ 12.5 g/L [29]. This tool is relatively easy to use compared to predecessors which had complex variables including intra-operative assessment, thereby limiting its application in clinical practice. Unlike older tools, this newer version has been validated with good performance in an external multi-institutional data set [30].

Strategies to minimize transfusions in hepatectomy

Bleeding is a common complication of hepatic resection and frequently results in the need for allogenic blood transfusion.

Table 1 Three-point transfusion risk score

1. Hemoglobin concentration < 12.5 g/dL
2. Primary liver malignancy
3. Major liver resection (> 3 segments)

Several peri-operative strategies have been reported to be effective in reducing the risk of significant hemorrhage during hepatectomy requiring RBCT (Table 2). Patient blood management (PBM), based on published evidence and best practice, improves post-operative morbidity, mortality, and resource utilization [31–33]. PBM programs focus on three pillars of care throughout the patient's peri-operative journey: the detection and treatment of pre-operative anemia, reduction of peri-operative blood loss, and harnessing and optimizing the patient-specific physiological reserve of anemia [34]. Recently, an expert consensus was established regarding PBM specific to patients undergoing liver resection, to support implementation in practice [35].

Pre-operative strategies

Pre-operative optimization of medical risk factors is important in reducing peri-operative transfusion requirements. Reviewing and correcting (where possible) biochemical parameters including serum albumin (a marker of overall nutritional status), hemoglobin, platelet count, and clotting studies (i.e., INR, PTT) in addition to timely stoppage and/or reversal

Table 2 Patient blood management protocol

Pre-operative strategies
1. Routine anemia work up (i.e., CBC[a], ferritin, transferrin saturation, vitamin B12, creatinine) during initial consultation for surgery
2. Oral iron in patients with iron deficiency anemia (serum ferritin < 30 μg/L or serum ferritin < 100 μg/L if transferrin saturation < 20%)
3. Intravenous iron in patients with oral iron intolerance or those < 4 weeks from surgery
4. EPO[b] should be reserved for patients with special blood needs (i.e., alloimmunization, refusal of RBCT[c], failure of iron therapy)
Intra-operative strategies
5. Pringle maneuver performed in 15–20 min intervals alternating with 5 min gaps for hepatic reperfusion
6. Clamp-crush technique: operative clamp used to compress the parenchyma and expose vessels/ biliary channels that are subsequently clipped, cauterized, ligated, or sealed
7. Fibrin, collagen, and oxidized cellulose agents (as per availability and experience)
8. Tranexamic acid
9. Low CVP[d] (≤ 5 cm H_2O) anesthesia in the pre-hepatic resection phase. Includes judicious use of fluids (< 1 mL/kg/h), accepting marginal urine output (25 cc/h), and Trendelenburg positioning (15^0)
10. Acute normovolemic hemodilution in patients at risk of major blood loss
11. Intra-operative cell salvage in patients with > 25% risk of RBCT[c]
Post-operative strategies
12. Consider RBCT[c] for Hb ≤ 75 g/L in the immediate post-hepatectomy period
13. Consider RBCT[c] for Hb ≤ 70 g/L in hemodynamically normal patients in the late post-operative period
14. Consider RBCT[c] for Hb ≤ 80 g/L in patients with CAD[e] in the late post-operative period

[a] CBC, complete blood count; [b] EPO, erythropoietin; [c] RBCT, red blood cell transfusion; [d] CVP, central venous pressure; [e] CAD, coronary artery disease

of anticoagulant and antiplatelet drugs is a crucial aspect of preparing a patient for liver surgery [36].

Iron

Pre-operative anemia is an established predictor of negative outcomes and peri-operative RBCT in patients undergoing major elective intra-abdominal surgery [37]. Pre-operative anemia should be routinely assessed at the time of the initial surgical consultation to facilitate its timely workup and treatment prior to the date of surgery. The work-up includes complete blood count for all patients, and ferritin, transferrin saturation, vitamin B12, and creatinine for patients with anemia. In order to avoid the need for patients to return for a second sample upon identification of anemia, consideration should be given to routine anemia work-up in all patients at the time of initial consultation [35, 38].

Iron deficiency, the most common cause of pre-operative anemia, is an easily modifiable risk factor, but is rarely addressed in practice. In a recent practice survey of general surgeons, nearly 51% of respondents were unlikely to conduct a pre-operative anemia workup. Further, half of the participants did not use pre-operative oral iron supplementation for anemia [39]. Despite equal short-term efficacy, IV iron has been shown to have less morbidity and better gastrointestinal tolerability than oral iron [40]. In a recent randomized controlled trial (RCT) of 72 patients, administration of IV iron reduced the need for blood transfusions by 60% compared to routine care and was associated with a shorter hospital length of stay, enhanced restoration of iron stores, and a higher mean hemoglobin concentration 4 weeks after surgery [41]. The administration of IV iron, therefore, can translate into significant benefits for the patient in the immediate post-operative period and several weeks thereafter, but is logistically more complex than oral supplementation. Therefore, current guidelines recommend prompt administration of oral iron in the pre-operative period for patients with iron deficiency anemia (serum ferritin < 30 μg/L or serum ferritin < 100 μg/L if transferrin saturation < 20%) [38]. Patients with oral iron intolerance or those less than 4 weeks away from surgery should be given IV iron for further pre-operative optimization [38].

Erythropoietin

The efficacy of other agents, including recombinant human erythropoietin (EPO), to avoid or reduce the need for RBCT has not been studied in patients undergoing hepatic resection. Current guidelines do not recommend the routine use of pre- or peri-operative EPO [38, 42, 43]. Such therapies should be reserved for patients with special blood needs (i.e., complex alloimmunization) or in a select population of patients who refuse RBCT or where iron therapy fails.

Intra-operative strategies

Intra-operative management of anemia and blood loss hinges on effective collaboration and communication including the surgical and anesthesia teams. Combining the best available evidence with expert multidisciplinary opinion suggests that it is appropriate to transfuse in the presence of significant intra-operative bleeding, ST segment changes, or an intra-operative hemoglobin of ≤ 75 g/L. It is inappropriate to transfuse for a hemoglobin of ≥ 95 g/L in the absence of significant bleeding or ST changes. Transfusion for a hemoglobin of ≥ 85 g/L requires strong justification and should by informed by a dialog between the surgical and anesthesia teams prior to transfusion [44]. Both surgical and medical strategies are often used in conjunction to minimize blood loss and reduce the need for RBCT.

Surgical techniques

Vascular occlusion Portal pedicle clamping (PPC) was first described by J.H. Pringle in 1908 [45]. The 'Pringle' maneuver involves manual temporary occlusion of portal venous and hepatic arterial inflow via a variety of different methods. Most commonly, intermittent PPC is performed in 10–20 min intervals alternating with 5 min gaps for hepatic reperfusion [46]. This has been shown to safely extend warm ischemic times up to 120 min. Selective inflow occlusion strategies have also been proposed to reduce the risk of ischemia to the remnant parenchyma, including hemi-hepatic inflow occlusion or total portal vein occlusion. These techniques require more advanced portal dissection, and the available trials have failed to demonstrate any clinical benefit over total inflow occlusion [47]. Other concerns about the safety of PPC with respect to progression of liver metastases secondary to ischemia-reperfusion have been refuted, including by a large matched cohort study demonstrating no differences in overall or recurrence-free survival in hepatectomy for colorectal liver metastases, with and without PPC [48]. A recent Cochrane review examining vascular occlusion during elective liver resections deemed PPC effective in significantly reducing blood loss compared to no vascular occlusion [49]. This technique is well tolerated in patients, appears to reduce blood loss during transection, and should be used liberally to reduce bleeding and need for RBCT in patients undergoing hepatic resection.

Total hepatic vascular exclusion (THVE) necessitates control and clamping of the infra- and supra-hepatic inferior vena cava [50]. This technique offers comparable levels of blood loss and transfusion requirements to PPC, but substantially increases operative hemodynamic instability (by hindering IVC flow and venous return to the heart), ischemic duration, hospital stay and post-operative complications such as pulmonary emboli [51]. A more selective approach, involving retrohepatic dissection and individual occlusion of the left,

middle, and right hepatic veins, offers decreased blood loss and transfusion requirements compared to PPC alone [52]. However, the complexity of this technique, as well as added operative time and potential for complications, has limited its use in clinical practice. THVE is not recommended for routine use and may only be indicated in special circumstances such as caval and hepatic vein resections, and in patients with elevated CVP (i.e., right-sided heart failure) [47]. A recent meta-analysis has deemed the evidence on this topic to be of low to very low quality [53].

Parenchymal transection techniques Hepatic parenchymal transection includes three components: dissection, vessel ligation and sealing, and management of the remnant liver surface. The finger fracture method is a traditional dissection technique that involves manual compression of the liver parenchyma to delineate vessels [54, 55]. The 'clamp-crush' method expands on the finger fracture method by utilizing an operative clamp to compress the parenchyma along the transection line, thereby exposing blood vessels and biliary channels that are subsequently clipped, cauterized, ligated or sealed [56]. New products including radiofrequency, ultrasonic, and water jet devices may be used as an adjunct for dissection in liver surgery.

Hydrojet devices employ pressurized water to dissect parenchyma and leave vasculobiliary structures for division, but have not been shown to decrease blood loss or RBCT transfusion [57]. Similarly, ultrasonic mechanical wave dissectors are theoretically appealing but have not been shown to offer better hemorrhage control [58]. One randomized study of 100 patients suggested that ultrasonic devices may in fact increase operative blood loss when compared the clamp-crush approach [57]. Their use, therefore, has not been shown to offer any benefit in decreasing morbidity or transfusion requirements during hepatectomy [59]. Radiofrequency devices use electromechanical waves to coagulate tissue, but evidence from at least two prospective randomized studies suggest that these devices can significantly increase post-operative complications in comparison to the clamp-crush technique [57, 60]. Therefore, its use is currently only recommended in the clinical trial setting [53]. In summary, despite several new options available for parenchymal transection, none have demonstrated consistent reduction in bleeding or RBCT. Furthermore, the clamp-crush technique is substantially cheaper than all of these methods [59].

Vessel and biliary ligation may be achieved mechanically using clips and ties, or using a variety of energy devices. Energy devices offer time-savings, but have not yet been shown to offer a significant reduction in blood loss and morbidity compared to mechanical methods [61]. Finally, vascular staplers may be used selectively for large vascular or biliary structures in combination with a parenchymal dissection technique, or in isolation for simultaneous compression and transection of parenchyma and vasculature. Although expeditious, full stapled hepatectomy may hinder precise dissection and results in increased costs compared to most other techniques [47, 62].

In summary, several combinations of instruments and techniques may be effectively used to dissect, seal, and divide hepatic parenchyma. None of these have been definitely shown to be superior to others, thus surgeons should develop comfort and expertise in one technique and learn to optimize this for their practice [35].

Hemostatic agents Biological and synthetic agents commonly used for hemorrhage control from the remnant liver include fibrin, collagen, and oxidized cellulose. Fibrin agents require preparation, with activating agents like calcium chloride and thrombin, prior to application [63]. Collagen agents can be applied in sheets and offer faster times to hemostasis than most other products [64]. Oxidized cellulose polymers function as absorbable patches that promote coagulation to achieve hemostasis [63]. A recent meta-analysis of five trials concluded that fibrin sealants may reduce the quantity of blood transfusions when compared to controls as well as oxidized cellulose products [53]. Combination studies examining the use of fibrin and collagen agents have failed to show an improvement in transfusion requirements compared to traditional techniques [65]. Most topical agents now include both fibrin and collagen, and while there are studies involving a multitude of commercially available products, differences in blood loss and transfusion requirements are based on low-quality evidence [53]. Their use, therefore, is surgeon dependent, and varies based on cost and hospital level availability of products [35].

Non-surgical therapies

Antifibrinolytics Administration of anti-fibrinolytic agents can help mitigate the hyper-fibrinolytic state related to systemic inflammation and hepatic injury during hepatectomy [66]. Plasmin inhibitors, such as aprotinin, are rarely used in clinical practice due to adverse effects on renal function and increased mortality when compared to plasminogen inhibitors such as tranexamic acid (TXA) [67]. TXA has been shown to reduce bleeding in various settings (trauma surgery, orthopedic surgery, spine surgery) [68], but its use in liver surgery has not been established. In one randomized trial of 214 hepatectomies, patients receiving 500 mg of intravenous TXA before surgery followed by 250 mg, every 6 h, for 3 days, had significantly lower amounts of operative blood loss and blood transfusion rates [69]. The ongoing multicenter Hemorrhage During Liver Resection: Tranexamic Acid (HeLiX; NCT02261415) trial is expected to shed further light on the role of intraoperative TXA administration for hemostasis during hepatectomy. Other agents such as recombinant factor VIIa have not been shown to reduce blood loss and

transfusion requirements in hepatectomy and should not be used outside of clinical trials or special circumstances [70, 71].

Low central venous pressure Low central venous pressure (CVP), generally ≤ 5 cm H_2O, reduces the impedance of blood flow from the hepatic venous system to the inferior vena cava, thereby reducing retrograde venous bleeding and offering improved hemostasis during hepatectomy [72]. Low CVP anesthesia is an established method of reducing intra-operative blood loss, transfusion requirements, and peri-operative morbidity in liver surgery [73]. The pre-hepatic resection phase is characterized by judicious use of intravenous fluids (< 1 mL/kg/h), accepting marginal urine output (25 cc/h) and Trendelenburg positioning (15^0) to increase venous return to the heart while maintaining a low CVP in the inferior vena cava [47, 74]. This method can lead to significant reductions in blood loss and transfusion requirements without any adverse effects on renal function and post-operative mortality [72].

Pharmacological interventions may be needed to achieve target CVP in this phase, including intravenous nitroglycerin, morphine, and furosemide [75]. Excessive hypotension (SBP < 90 mmHg) may need correction with small corrective boluses of crystalloid solution and/ or vasopressor agents such as Dopamine [47]. While hypoventilation can also aid in CVP reduction by lowering intrathoracic pressures, a randomized controlled trial failed to demonstrate a beneficial effect on bleeding during hepatic resection [76].

The post-resection phase consists of fluid resuscitation, targeting euvolemia to normalize blood pressure and urine output. Routine CVP monitoring (via central venous catheterization) is not routinely recommended in either the pre- or post-hepatic resection phase of intra-operative fluid management [77].

Hemodilution Acute normovolemic hemodilution (ANH) involves pre-operative removal and storage of a calculated volume of the patient's blood. Euvolemia is maintained by replacing blood volume with varying mixtures of crystalloid and colloid solutions. Allowable blood loss is determined using an established formula: $V_L = EBV \times H_0 - H_F/H_{AV}$, where V_L is the allowable blood loss, EBV is the estimated blood volume, H_0 is the patient's initial hemoglobin, H_F is the patient's minimal allowable hemoglobin, and H_{AV} is the average of the initial and minimal allowable hemoglobin [78]. Upon reaching a previously established transfusion threshold, stored autologous blood is reinfused with the goal of minimizing the use of allogenic blood. In a RCT of 130 patients, ANH reduced the overall allogenic red cell transfusion rate by 50% compared with standard anesthetic techniques. These benefits were most pronounced in patients with > 800 mL blood loss. Notably, the low CVP technique was used in both arms of this study. ANH patients also had significantly higher post-operative hemoglobin levels and required fewer red cell units overall [79]. The use of ANH should be considered in hepatectomy patients deemed to be at risk of major blood loss [79].

Phlebotomy Phlebotomy involves removal of 7–10 mL per kg of body weight of whole blood, with an aim to decrease CVP and establish a state of relative hypovolemia. The removed blood is not replaced by intravenous fluid administration and is transfused back at the end of the liver parenchymal transection, or within 8 h of collection [80]. The safety and feasibility of this technique is well-demonstrated in the literature. In a prospective sample of 138, phlebotomy with controlled hypovolemia was shown to be significantly protective of peri-operative transfusions, compared to low CVP anesthesia alone [80]. The ongoing Phlebotomy Resulting in Controlled Hypovolemia to Prevent Blood Loss in Major Hepatic Resections (PRICE) trial (NCT02548910) is expected to shed further light on the clinical utility of phlebotomy in minimizing transfusions after hepatectomy.

Autologous blood recycling Autologous blood recycling is a way of recovering blood lost during surgery and re-infusing it into the patient. Intra-operative cell salvage (ICS) is efficacious in reducing the need for allogenic blood transfusions in adult elective surgery [81]. There remains controversy around the use of ICS in hepatectomy for cancer, due to the risk of systemic dissemination of malignant cells. A meta-analysis of observational studies, however, did not demonstrate any association between ICS and cancer recurrence [82]. Routine use of ICS has been shown to be cost-minimizing during liver resection, especially in patients with > 25% risk of blood transfusion, and may be considered in this setting [83].

Post-operative strategies

In the immediate post-operative period, patients must be carefully monitored for post-operative bleeding, reflected by changes in clinical and biochemical parameters. Maintaining normothermia [84], correcting coagulopathy in the presence of active bleeding [85], and ensuring adequate nutrition [86] all reduce the rate of allogenic blood transfusions and its associated risks. It is important to note that PT-INR is an inadequate predictor of functional coagulation in the post-hepatectomy population and should not be used to guide the decision to transfuse FFP or to initiate or delay thromboembolic prophylaxis [87].

Post-operative transfusions

Combining the best available scientific evidence with multidisciplinary expert opinion suggests that it is appropriate to transfuse for a Hb of ≤ 75 g/L, in the immediate post-

hepatectomy period [44]. A more restrictive transfusion strategy is recommended for patients in the late post-operative period. Hemodynamically stable patients without coronary artery disease (CAD) should be transfused at a Hb of ≤ 70 g/L. Those with CAD may benefit from the additional oxygen carrying capacity, and should be transfused at a Hb of ≤ 80 g/L [44, 88, 89]. It is also recommended that a single unit of packed red cells be administered at a time, and that hemoglobin and symptoms be reassessed following transfusion prior to administering additional units [35, 90, 91].

Implementing a systematic multi-pronged protocol to reduce intra-operative blood loss and subsequent blood transfusions may be effective in reducing the morbidity and mortality associated with hepatic resections.

Conclusion

Hemorrhage during hepatectomy is associated with substantial post-operative morbidity. It may also impact long-term outcomes such as disease-free recurrence, disease-specific survival and overall survival. As such, a concerted effort is needed to minimize bleeding and blood transfusion using pre-operative, intra-operative (surgical and non-surgical), and post-operative strategies.

Compliance with ethical standards

Conflict of interest Dr. Karanicolas holds a research grant from Baxter to study Hemopatch in patients undergoing distal pancreatectomy and has received speaker honoraria from Sanofi. Dr. Hallet has received speaking honoraria from Ipsen Biopharmaceuticals Canada and Novartis Oncology. Dr. Latchana and Hirpara have nothing to disclose.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

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