Hemostasis and Hepatic Surgery

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KEYWORDS

• Liver resection • Blood loss • Blood transfusion • Hemostasis • Vascular occlusion • Parenchymal transection • Topical hemostatic agents • Low central venous pressure

KEY POINTS

- Operative blood loss and allogeneic transfusions are independently associated with worse perioperative and long-term outcomes following hepatectomy.
- Restrictive transfusion protocols are safe and effective at minimizing exposure to allogeneic blood in surgical patients.
- Maintenance of low intraoperative central venous pressure is associated with decreased operative blood loss.
- Vascular inflow occlusion is well tolerated and can decrease blood loss during hepatectomy.
- Topical hemostatic agents may decrease intraoperative blood loss from the remnant surface.

INTRODUCTION

The liver hosts the most complex vascular anatomy of any human organ. Liver resection was once deemed an impossible feat largely because of its propensity for hemorrhage, but is now the mainstay for the treatment of primary and secondary tumors of the liver.

Significant progress in anatomic approaches, surgical technique, diagnostic imaging, and perioperative care has led to vast improvements in outcomes of patients undergoing hepatic resection. In the 1970s, operative mortality from hepatic resection occurred in approximately 20 to 30% of patients.[1] Contemporary series now report rates of major morbidity and mortality in high-volume centers to be less than 40% and 5%, respectively.[2,3] Despite these improvements, bleeding continues to be a major source of morbidity for patients and remains a pervasive challenge to hepatic surgeons. Intraoperative blood loss averages between 200 and 2000 mL for major

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hepatic resection, and perioperative blood transfusions are used in 20% to 50% of patients.[2,4,5] Operative blood loss and exposure to allogeneic blood are independently associated with worse perioperative and long-term outcomes in patients undergoing hepatic resection.[2,3,6,7] These observations highlight the paramount importance of minimizing blood loss and blood transfusion in hepatic surgery. This review discusses strategies to minimize blood loss and the utilization of blood transfusion pertaining to oncologic hepatic surgery.

ALLOGENEIC RED BLOOD CELL TRANSFUSION IN HEPATIC RESECTION

The development of modern blood banking has contributed significantly to the improvements in outcomes in hepatic surgery and greatly expanded what is technically feasible for hepatic surgeons. Allogeneic blood transfusion is necessary in cases of severe hemorrhage to maintain hemodynamic stability and end-organ perfusion. However, blood transfusions carry risks of infectious disease transmission, transfusion reaction, and immune suppression and contribute notable economic costs. Furthermore, immunosuppression attributable to allogeneic transfusion has been strongly linked to increases in postoperative infectious complications and cancer recurrence.[3,6,8,9]

The evolution of surgical techniques has led to a reduction in blood loss and transfusion requirements, but paradigm shifts in transfusion strategies have further contributed to these trends. Randomized controlled trials have demonstrated that restrictive transfusion strategies are at least equivalent if not superior for patients who are critically ill, undergoing major elective surgery, or suffering from acute hemorrhage.[10–12] Specific transfusion triggers in surgical patients remain somewhat elusive, although consensus guidelines generally suggest consideration of transfusion in asymptomatic, hemodynamically stable patients with a hemoglobin lower than 6 to 8 g/dL.[13,14] Our institutional practice is to transfuse for a hemoglobin less than 7 g/dL in the asymptomatic nonbleeding patient. Considerable reductions in unnecessary blood transfusion are achievable through implementation of institutional transfusion policies.[15]

NONOPERATIVE TECHNIQUES TO MINIMIZE BLOOD LOSS DURING HEPATIC RESECTION

Improvements in outcomes of hepatectomy are not solely attributable to refinements in surgical techniques. Anesthetic and perioperative care have made substantial contributions to the progress of hepatic surgery.

Low Central Venous Pressure Anesthesia

The strategy of maintaining a low central venous pressure (CVP) during liver resection is based on the premise that blood loss during hepatectomy is derived largely from backflow from the vena cava and hepatic veins. As such, blood loss is exacerbated by normovolemic or hypervolemic states that result from aggressive fluid resuscitation. Decreased blood loss, transfusion requirements, and perioperative morbidity have been demonstrated with the use of low CVP anesthesia.[16–19] With the strategy of low CVP anesthesia, the procedure is divided into the (1) pretransection phase and the (2) posttransection phase.[16] During the pretransection phase, a low CVP (<5 mm Hg) is accomplished primarily through volume restriction. Intravenous fluids are limited (<1 mL/kg per hour) and marginal urine output (25 mL/h) is accepted. Trendelenburg positioning (15°) is used to increase venous return to the heart while decreasing CVP in the inferior vena cava.

A number of pharmacologic adjuncts may assist achieving a low CVP, including loop diuretics, intravenous nitroglycerin, and morphine, although with judicious fluid management these are rarely required. Hypoventilation has been suggested to aid in CVP reduction by lowering intrathoracic pressures, but the results of a randomized controlled trial failed to demonstrate any difference in bleeding, despite modest reductions in CVP.[20] Clamping of the infrahepatic inferior vena cava has also been proposed as a measure to decrease CVP and has been shown to significantly reduce blood loss in randomized controlled trials.[21,22] One of these trials demonstrated a statistically significant increase in symptomatic pulmonary embolism, tempering enthusiasm for this technique.[21]

The development of hypotension may necessitate the administration of vasopressors (eg, dopamine) or small corrective fluid boluses to target a systolic pressure of greater than 90 mm Hg. Other safety concerns include air embolus and organ hypoperfusion (eg, renal insufficiency) due to prolonged hypotension, yet these have not been substantiated.[16,19]

The posttransection phase commences once the specimen has been removed and hemostasis is achieved. This phase is characterized by restoration of euvolemia with fluid resuscitation and normalization of blood pressure and urine output. This strategy has clearly been associated with decreased operative blood loss and is accompanied by a good safety profile when performed by a capable hepatobiliary team.

Autotransfusion Strategies

Three main strategies of autotransfusion have been described: (1) preoperative autologous blood donation (PABD), (2) acute normovolemic hemodilution (ANH), and (3) intraoperative cell salvage (ICS).

Preoperative autologous blood donation requires patients to donate blood in advance of surgery that can then be transfused in the perioperative period. Several limitations have restricted the use of this technique, including high processing costs and the time interval necessary for the patient to reconstitute blood stores between donation and surgery. In patients undergoing hepatic resection, PABD does not appear to reduce the need for allogeneic blood or improve perioperative outcomes.[23,24] Furthermore, the economics of PABD programs are unjustifiable when one considers that 50% to 60% of donated units are discarded.[25]

ANH involves the removal of whole blood from patients immediately before surgery and autotransfusion during the posttransection phase. The premise of ANH is that shed blood contains a lower red cell mass due to the hemodilution and can reduce the need for allogeneic transfusion. Euvolemia is restored with crystalloid or colloid resuscitation to target a hemoglobin of 8 g/dL or a hematocrit approximately 24%. The whole blood is stored at room temperature in the operating theater and is retransfused intraoperatively if a transfusion trigger is encountered (typically $<$7 g/dL) or at the termination of surgery. The removed volume of whole blood can be calculated by using the following formula:

$$V_L = EBV \times (H_0 - H_F/H_{AV}),$$

Where V_L is allowable blood loss; EBV, estimated blood volume; H_0, initial Hgb; H_F, minimal allowable Hgb; and H_{AV}, average of initial and minimal allowable Hgb.

A meta-analysis including 4 randomized trials of ANH demonstrated a significant reduction in requirements for allogeneic transfusion (relative risk [RR] 0.41; 95% confidence interval 0.25–0.66).[19] ANH avoids the high processing costs of PABD, risks of clerical error, and degradation associated with blood storage. Conversely, the technique is quite labor-intensive and can lead to transient hypotension. The benefit of

ANH is most pronounced in patients with operative blood loss that exceeds 800 mL and its use should be considered in patients deemed to be at risk of major blood loss.[26]

Intraoperative cell salvage with autotransfusion is routinely used in high blood loss procedures with demonstrable reductions in need for allogeneic transfusions.[27] Shed blood is collected intraoperatively and filtered before being autotransfused. Due to the theoretic concerns of dissemination of malignant cells, ICS has not been widely used during oncologic surgery. A recent systematic review, however, failed to identify any evidence that ICS increases the risk of tumor recurrence, suggesting that ICS in oncologic surgery should be more carefully considered.[28]

Pharmacologic Strategies to Minimize Bleeding

Several pharmacologic agents are available to reduce bleeding and transfusion requirements in surgery. The main drug classes include (1) antifibrinolytics and (2) procoagulants.

Antifibrinolytic agents inhibit plasmin directly (eg, aprotinin) or block the conversion of plasminogen to plasmin (eg, tranexamic acid and epsilon aminocaproic acid). These agents have been extensively studied in high blood loss procedures, including liver transplantation, where they have demonstrated reduction in blood loss and transfusion requirements with acceptable safety profiles. Additionally, concerns regarding the risk of thromboembolic complications have not been demonstrated in large prospective trials.[29] Fewer trials have evaluated the effect of antifibrinolytics on hemostasis in elective hepatic resection, but both tranexamic acid and aprotinin appear to reduce blood loss and transfusion requirements in small randomized studies.[30,31] The ongoing HeLiX trial (Hemorrhage During Liver Resection: traneXamic Acid; ClinicalTrials.gov ID: NCT02261415) is currently investigating the effect of tranexamic acid in the setting of a multicentered randomized placebo-controlled clinical trial.

Impairments in coagulation due to underlying liver disease (eg, cirrhosis) or due to extensive hepatectomy have encouraged the study of procoagulant agents in controlling perioperative bleeding. The most noteworthy agents include recombinant factor VIIa, antithrombin III, and desmopressin, all of which have been investigated in randomized controlled trials with disappointing results.[5] Although the safety of procoagulants has been surprisingly favorable, none of these drugs has demonstrated clinical benefits with regard to bleeding endpoints in patients undergoing hepatic resection and are therefore not recommended.

OPERATIVE STRATEGIES TO MINIMIZE BLOOD LOSS

Vascular Occlusion Techniques

Occlusion of the inflow vessels by encircling and compressing the portal pedicle was first reported by Pringle[32] for the arrest of hemorrhage in the setting of liver trauma. The hemodynamic effects of pedicular clamping are minimal, and periods of warm ischemia up to 60 minutes are well tolerated in patients with healthy liver parenchyma. Various modifications have been proposed to minimize blood loss during parenchymal transection and mitigate the risks of ischemia-reperfusion injury to the liver remnant. Belghiti and colleagues[33] established the safety and improved tolerance of intermittent pedicular clamping achieved with 15-minute to 20-minute clamping alternating with 5-minute reperfusion periods. With intermittent clamping, total warm ischemic times can be safely extended up to 120 minutes.[33] Selective inflow occlusion strategies have been proposed to reduce the risk of ischemia to the remnant parenchyma, including hemihepatic 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.[34]

Despite the intuitive appeal of inflow occlusion, the evidentiary basis is conflicting and based on a few small prospective controlled studies. Three small trials have reported modest improvements in blood loss and transfusion rates in patients randomized to intermittent Pringle maneuver.[35–37] This is in contrast to 2 more recent trials that have demonstrated no difference in blood loss or transfusion rates with vascular inflow occlusion.[38,39] No available trials have been adequately powered to address the impact of pedicle clamping on major morbidity or mortality. As such, published meta-analyses report conflicting findings with regard to the benefits of vascular inflow occlusion.[34,40] Overall, vascular inflow occlusion is well tolerated in patients, appears to reduce blood loss during transection, and should be used liberally to reduce bleeding and need for transfusion in patients undergoing hepatic resection.

A notable shortcoming of inflow occlusion alone is that major bleeding during liver resection can result from backflow through the hepatic veins. Various techniques have been proposed to control vascular outflow, which in conjunction with inflow control are referred to as hepatic vascular exclusion (HVE). These strategies are particularly suited for tumors abutting or involving the hepatic veins or vena cava or in patients with elevated CVP (eg, right-sided heart failure). Although the liver is excluded from the systemic circulation, the blood flow within the vena cava is also interrupted, which can result in significant hemodynamic sequelae. The available trials that have compared total HVE with inflow occlusion alone revealed no difference in blood loss, transfusion rates, liver failure, or mortality.[34] Operative times, length of stay, and intraoperative hemodynamic changes, however, were significantly greater in patients receiving HVE. In an effort to avoid the physiologic effects of caval interruption, selective HVE has been used whereby the hepatic veins are encircled extraparenchymally, leaving the caval inflow intact. Despite better physiologic tolerance, selective HVE is technically demanding and potentially hazardous, and is of no value in tumors that encroach on the hepatocaval junction. For routine hepatic resection, HVE is not recommended given its technical requirements, hemodynamic effects, and comparable clinical outcomes.

Parenchymal Transection

Transection of the liver parenchyma is responsible for most blood loss attributable to hepatectomy. Transection requires the careful exposure of vascular and biliary structures followed by division and sealing. The traditional technique against which newer techniques are compared is the clamp-crush technique (a refinement of the finger-fracture technique). This technique involves the controlled crushing of parenchyma, leaving behind exposed blood vessels and biliary channels that are subsequently clipped, ligated, cauterized, or otherwise sealed. Numerous devices have been devised to improve on the performance characteristics of liver transection, including blood loss, biliary leak, and transection time. Several small randomized trials have been conducted with this objective in mind, but none have clearly demonstrated superiority of any technique.[41,42] In practice, this is reflected by the enormous variation in the utilization of these devices among hepatobiliary surgeons (**Table 1**).[43]

Other commonly used techniques for dissection of vasculobiliary structures include the ultrasonic dissector and water-jet dissector. Ultrasonic dissection offers excellent quality of visualization of blood and biliary vessels. Division of the parenchyma is achieved using an oscillating tip that causes fragmentation of hepatocytes, sparing collagen-rich blood vessels and biliary structures. The hand piece is coupled with a saline irrigator and aspiration system that removes cellular debris from the surgical

Table 1
Comparison of parenchymal transection techniques

	Technique	Characteristics
Dissection	Clamp-crush technique	• Simple, reliable method • No specialized equipment required • Permits good exposure of vascular and biliary structures
	Ultrasonic dissection	• Excellent visualization of vascular and biliary structures • No vessel-sealing or coagulation functionality • Time consuming
	Water-jet dissection	• Precise, tissue-selective dissection of vascular and biliary structures • No zone of tissue injury • No vessel-sealing or coagulation function
Vessel ligation	Clip/ties	• Simple method • Time consuming
	Bipolar electrothermal vessel sealer	• Coagulates, seals and divides tissue • Decreased transection time demonstrated in some studies[51] • Meta-analysis suggested decrease in blood loss, biliary leak and hospital stay compared with CC[47]
	Radiofrequency dissecting sealer	• Coagulates and seals zone of tissue • Maintains low tissue temperatures • No difference in blood loss or tumor recurrence compared with CC[44] • Higher infective and bleeding complications when compared with CC[42]
	Stapler transection	• Faster transection with comparable blood loss compared with CC[52] • Concerns that staples inadequately seal small biliary channels • Highly costly

CC refers to traditional clamp-crush method with clips/ties alone for vessel ligation.
Data from Refs.[42,44,47,51,52]

plane. Water-jet dissection uses a high-velocity laminar water jet to allow precise dissection of hepatic parenchyma with preservation of fibrous structures in the absence of a surrounding zone of cellular injury. The water jet is favored by many surgeons for its utility in the exposure of major pedicles and hepatic veins. The limited available trials do not show any technique to be clearly superior and the choice currently remains a matter of surgeon preference.[44–46]

Ligation of intraparenchymal vasculobiliary structures can be achieved with a similar variety of techniques. Bipolar electrothermal vessel sealers are attractive, as they are able to seal and divide vessels up to 7 mm in diameter. Despite theoretic concerns of improper sealing of biliary channels, no trials have demonstrated an increase in postoperative bile leaks.[47] Radiofrequency dissecting sealer devices have also been suggested to offer improved hemostasis by creating a region of ablation that is subsequently transected. Of potential concern, radiofrequency-assisted techniques generate a zone of coagulation on each side of the planned transection plane, resulting in additional tissue loss. Although very few well-conducted trials have evaluated radiofrequency devices in hepatic resection, the available data suggest that it offers

Table 2
Summary of topical hemostatic agents

Topical Hemostatic Agent	Active Component	Selected Examples
Matrix agents	Collagen Cellulose Gelatin Microporous polysaccharide spheres	Avitene, Instat Surgicel Gelfoam, Surgifoam Arista
Coagulation factor-based agents	Fibrin sealant (fibrinogen and thrombin) Topical thrombin	Tisseel Evithrom
Combination agents	Gelatin/Thrombin Collagen/Fibrinogen/Thrombin	Floseal, Surgiflo TachoSil

modest reductions in blood loss but is associated with increased postoperative abscess formation and possibly more frequent bile leaks.[48–50]

Management of the Remnant Surface

Hemorrhage from the raw liver surface can lead to significant blood loss in the post-transection and postoperative phases. Meticulous inspection of the cut surface of the liver remnant allows identification of small blood and biliary vessels that can be controlled with ligation, clips, or other sealing techniques. Topical hemostatic agents are adjuncts commonly used to facilitate the development of a stable coagulum to seal the cut surface of the remnant. Available agents can be broadly classified as (1) hemostatic matrix agents, (2) coagulation factor-based agents, and (3) combination agents (**Table 2**). Matrix agents provide a scaffold for endogenous coagulation to occur and contain no active coagulation factors. These matrices are typically composed of oxidized cellulose, microfibrillar collagen, microporous polysaccharide spheres, or gelatin. The coagulation factor–based agents are the most common topical hemostatic agents currently in use by liver surgeons.[53] These compounds typically contain fibrinogen or thrombin along with various compositions of coagulation cofactors (eg, calcium, factor XII, aprotinin) and serve to reenact the endogenous coagulation cascade. Fibrinogen is converted to fibrin by thrombin as a final stage of the coagulation cascade, permitting the formation of clot. Topical thrombin is also available and is similarly applied to activate endogenous fibrinogen. Many of the commercially available agents are combination agents that contain both active hemostatic components and a coagulation matrix.

Fibrin sealants reduce time to hemostasis and increase rates of complete intraoperative hemostasis.[54] There is no definitive evidence that any topical hemostatic agent decreases clinically significant outcomes, such as blood loss, transfusion, and perioperative morbidity in liver resection, although few studies are adequately powered for these endpoints.[40,53] Furthermore, little evidence exists to suggest whether combination agents are more efficacious than matrix agents alone.[55–57] The interpretation of the available evidence is complex due to the quality of studies and diversity of topical hemostatic agents. The data appear to suggest that intraoperative blood loss can be improved with topical hemostatic agents, yet the superiority of any one agent has not been demonstrated and the substantial costs of many of these agents have not been justified.

SUMMARY

Although outcomes following hepatectomy have improved substantially over time, blood loss continues to pose a challenge to liver surgeons. Perioperative blood loss and allogeneic transfusion are clearly associated with inferior short-term and long-term outcomes in patients. With modern approaches and techniques, blood loss can be minimized and allogeneic transfusion can be avoided in the vast majority of patients undergoing major hepatic resection. The techniques described herein and their appropriate application should be familiar to the hepatic surgeon to ensure best outcomes in patients undergoing hepatic resection.

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