Review

Patient Blood Management in Hepatobiliary and Pancreatic Surgery

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Despite improved perioperative management and surgical techniques, patients undergoing hepatobiliary and pancreatic (HBP) surgery often need to be transfused. Although disadvantages of transfusion and advantages of patient blood management (PBM) have been recognized, study results of the effects of PBM in HBP surgery are rare. The aim of this article was to review the current status of PBM in Korea in patients having HBP surgery. PBM in HBP surgery consists of increasing preoperative hemoglobin level, preoperative blood conservation, and preoperative autologous blood donation. The main intraoperative modalities used to conserve blood in recent studies were autologous techniques of acute normovolemic hemodilution and intraoperative cell salvage (Cell Saver®). In postoperative PBM, blood augmentation with erythropoietin and iron are also used depending on the postoperative hemoglobin level. Advances in surgical, anesthesiologic and pharmacologic strategies have contributed to a reduction of blood loss during HBP surgery in all patients.

Key words: Blood management; PBM; Transfusion

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INTRODUCTION

Patients undergoing hepatobiliary and pancreatic (HBP) surgery often need to be transfused, despite advances in surgical skills and perioperative care. However, many studies have indicated that cancer patients who are transfused have higher rates of perioperative mortality and cancer recurrence, and poorer prognoses [1]. Moreover, viral or bacterial infections, immunologic reactions, and increased postoperative morbidity are other adverse consequences of allogeneic transfusions. Furthermore, since there are not enough blood donors in Korea to supply the demand, new treatment strategies for HBP patients are needed.

Patient blood management (PBM) programs, medical care without allogeneic blood transfusion, have traditionally been applied in various clinical situations, e.g., when patients refuse to be transfused for religious reasons, when there is no blood to transfuse, and when safe blood is not available [2]. Although PBM is a relatively new technology in the field of HBP surgery, its general concepts are very similar to those of traditional PBM. The basic concepts of PBM applicable to the perioperative and intraoperative method have recently been described. Erythropoietin, ferritin, vitamin B12, or volume expanders and preoperative autologous blood donation (PAD) are used in perioperative PBM. Intraoperative management includes acute normovolemic hemodilution (ANH), cell salvage (Cell Saver®), and hypotensive anesthesia.

Although the disadvantages of transfusion and the advantages of PBM are widely recognized, few studies have evaluated the beneficial effects of PBM in HBP surgery. Although the use of PBM in HBP operations without transfusion (including pancreaticoduodenectomy for periampullary lesions, living donor liver transplantation, and major hepatectomy) has been reported in the past few years, it is inherently challenging to carry out researches on transfusion-related issues because reasons and sequelae of transfusion are multifactorial [3-6]. The goal of this article is to review the current status of PBM programs in HBP surgery.

CURRENT STATUS OF TRANSFUSION IN HBP SURGERY

There is a higher likelihood of transfusion in HBP surgery compared to any other operations for the following reasons. First, most HBP operations require challenging and complex operative techniques. Although technical improvements have led to a reduction in blood product requirements, allogeneic blood transfusions are still required in many cases. Second, of patients undergoing HBP, especially those with liver diseases have underlying anemia, thrombocytopenia due to splenomegaly, coagulopathy, and effective hypovolemia. This also makes performing HBP surgery without blood transfusion difficult.

According to a recent report based on public use files from the American College of Surgeons National Surgical Quality Improvement Program, about 25% of patients undergoing HBP surgery received at least one pack of red cells during the perioperative period. There were large differences in the frequency of transfusion needed among different types of HPB surgery: hepatic wedge resection 18.7%, lobectomy 31.3%, trisegmentectomy 39.8%, distal pancreatectomy 19.8%, Whipple 28.7%, and total pancreatectomy 43.6% [7].

In addition, investigators at the Memorial Sloan-Kettering Cancer Center reported an estimated average blood loss of 400 mL during hepatectomies (range 100 to 1,500 mL) and also 400 mL during pancreatectomies (range 250 to 1,800 mL).

According to recent reports published in Korea, intraoperative transfusion was required in 57% of patients undergoing pancreaticoduodenectomies, in 31% of laparoscopic pylorus-preserving pancreaticoduodenectomies, in 29% of laparoscopic hepatectomies, in 24.5% of laparoscopic major liver resections, and in 9% of patients undergoing left hemihepatectomies [8-13]. Also, reports on liver resection and pancreaticoduodenectomies without transfusion in Korean patients have been published by our group [3,14].

As we mentioned above, transfusion is still often needed in HBP surgery despite improved blood management techniques and materials. PBM standards consist of optimization of hemoglobin (Hb) in the preoperative period, blood-conservation methods, detailed skills in reducing bleeding during the intraoperative period, and thorough care in the postoperative period, which have improved results of major HBP surgery (Table 1).

MANAGEMENT OF PERIOPERATIVE ANEMIA IN HBP SURGERY

Preoperative PBM in HBP surgery includes increasing Hb levels, blood conservation, and autologous blood donation in the preoperative period. Patients with low Hb levels ahead of surgery are likely to undergo allogeneic transfusion. Erythropoietin, often used with iron sulfate, can be utilized to increase hemoglobin levels in the preoperative period even in the absence of anemia [8]. In a recent study, a strategy of reaching preoperative Hb >12 g/dL by blood augmentation has been applied for PBM in HBP surgery [6]. We actually have used this 'Rule of 12', a strategy to increase preoperative Hb to 12 g/dL with erythropoietin, iron sulfate, etc. Our protocol is shown in Fig. 1. In HBP surgery, because the average intraoperative blood loss is approximately 500 mL to 1,000 mL, a preoperative Hb level of 12 g/dL would be safe and appropriate for PBM. PAD is a method for preserving the patient's own blood with careful control of anticoagulation, including discontinuation or replacement of agents that could inhibit clotting [2]. The goal of PAD is to provide safe blood for patients who may need a blood transfusion in the perioperative situation. Another goal of PAD is to induce stimulation of erythropoiesis, resulting in an increase in the patient's total red blood cell (RBC) mass before scheduled elective surgery. However, PAD is a difficult procedure compared to allogeneic blood transfusion and is not yet free from risks of infection. Moreover, cost, patient's inconvenience, and risk of medical accidents are reasons why the choice of PAD has declined recently.

Blood augmentation with erythropoietin and ferritin is also used in postoperative PBM in HBP surgery depending on the postoperative Hb level. In addition, prophylaxis against stress ulceration using H2 receptor antagonists or proton pump inhibitors, and minimization of blood testing, are frequently used strategies for PBM in HBP surgery [15].

Table 1. Principles of management for transfusion-free HBP surgery

Preoperative	Increasing preoperative Hb levels
	Preoperative blood conservation/preoperative autologous blood donation (PAD)
Intraoperative	Acute normovolemic hemodilution
	Intraoperative cell salvage (Cell Saver®)
	Surgical skills such as inflow occlusion
	Anesthetic techniques such as the use of the low CVP
Postoperative	Blood augmentation
	Prophylaxis against stress ulceration
	Minimization of blood testing

<table>
<tr><td colspan="4" align="center">Check Preoperative Hb(g/L)

Check Anemia data*</td></tr>
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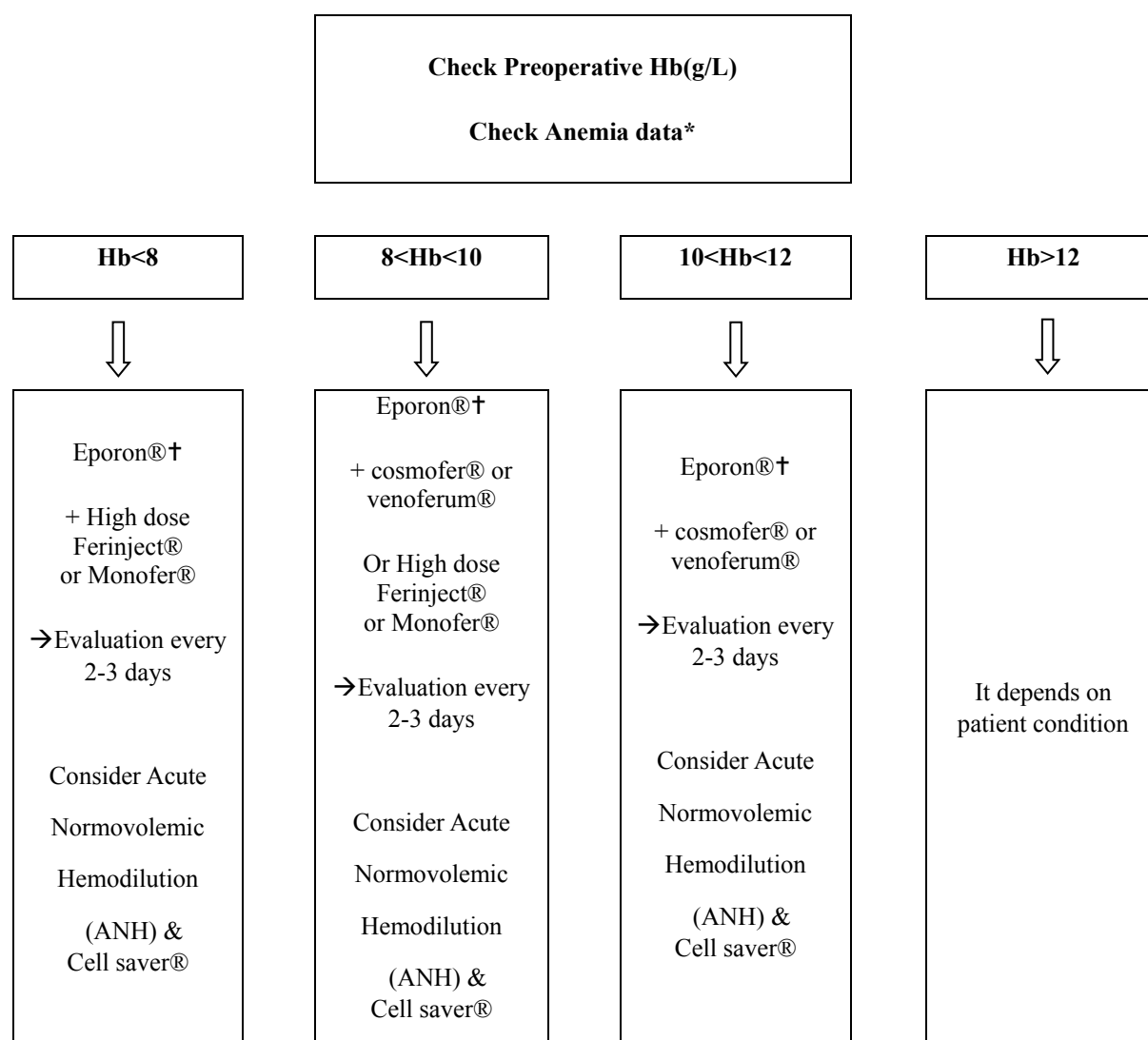| Hb<8	8<Hb<10	10<Hb<12	Hb>12
Eporon®† + High dose Ferinject® or Monofer® →Evaluation every 2-3 days Consider Acute Normovolemic Hemodilution (ANH) & Cell saver®	Eporon®† + cosmofer® or venoferum® Or High dose Ferinject® or Monofer® →Evaluation every 2-3 days Consider Acute Normovolemic Hemodilution (ANH) & Cell saver®	Eporon®† + cosmofer® or venoferum® →Evaluation every 2-3 days Consider Acute Normovolemic Hemodilution (ANH) & Cell saver®	It depends on patient condition

Fig. 1. Preoperative protocol for HBP patients ('Rule of 12', Hanyang University). Figure presents the strategy for preoperative management according to preoperative hemoglobin. Eporon®, Ferinject®, Cosmofer® and Venoferum® are used selectively according to preoperative hemoglobin, and the target for determining the treatment plan is set at 12 g/L hemoglobin. *Before giving erythropoietin or iron sulfate, we examine anemia data to evaluate and identify the cause of anemia. Data include iron, total iron-binding capacity, ferritin, reticulocytes, peripheral blood cell morphology. †Eporon®: Erythropoietin, Ferinject®: Iron carboxymaltose, Monofer®: Iron isomaltoside, Cosmofer®: Iron dextran, Venoferum®: Iron sucrose.

STRATEGY TO REDUCE BLEEDING DURING OPERATION

The major intraoperative methods used to save patient's own blood in recent studies are the autologous procedure of ANH and cell salvage (Cell Saver®). These methods have been applied with success to patients who refuse to be transfused for any reason, when transplantation of liver or live donor hepatectomies are required [4].

In ANH, blood is collected after putting the patient under anesthesia in advance of surgery. Then, the collected blood is replaced by crystalloid and/or colloid fluids to maintain the intravascular volume. Consequently, the consistency of the blood during surgery is reduced and blood loss during perioperative period can be reduced. For example, the Memorial Sloan-Kettering group has described their practice with ANH in 2 randomized controlled studies that resulted in a reduced frequency of transfusion for hepatic resections. Nonetheless, there was little clinical improvement among patients submitted to pancreaticoduodenectomy, compared to the results of standard intraoperative management [16]. ANH has a number of

substantial advantages over PAD. It is suitable for both emergent and elective operations because of the minimal preoperative preparation time and avoidance of patient discomfort [2]. Furthermore, it is safe, and patients who refuse transfusion can potentially benefit from its use.

Intraoperative cell salvage (Cell Saver®) involves recovering the patient's blood loss during surgery by washing and returning the blood to the patient [2]. It could be an effective method for blood conservation in surgical procedures that cause excessive bleeding and could be useful in cases where allogeneic blood transfusion is not available on religious grounds. Intraoperative cell salvage (Cell Saver®) would be acceptable to patients refusing transfusion on religious grounds because its circuitry is designed to remain connected with the patients' own circulatory systems. It is a representative example of a safe and effective technique [17]. Recently, a concern that hidden cancer cells in the blood might cause dissemination of cancer during surgery has grown. However, a meta-analysis of studies of intraoperative blood salvage has found that recurrence rates are not especially high [18].

The main reduction of intraoperative bleeding has been due to progress in surgical and anesthetic skills, and a better understanding of hemostatic disorders in HBP patients. For example, a surgical technique (called the Pringle maneuver) of occluding the inflow of blood to the liver by clamping the hepatic artery and portal vein, and the anesthetic technique of using a central venous pressure (CVP) of <5 cm H_2O, are clear and effective methods for reducing the loss of blood during HBP surgery [19].

NEW METHODS OF BLOOD MANAGEMENTIN HBP SURGERY

Progress in surgical skills, anesthesiologic techniques, and pharmacologic procedures has made a major contribution to decreasing the loss of blood during HBP surgery [20]. Since comparative data on the various techniques of HBP surgery are not yet available, the technique to use is usually determined and chosen by the individual surgeon [21]. However, some recommendations have been made in recent years. In addition to the vascular occlusion techniques used especially in liver surgery, several new methods and devices have been developed for HBP surgery.

Since the introduction of the first successful pancreaticoduodenectomy by Whipple in 1921, pancreaticoduodenectomy has been increasingly performed for patients who have malignant or benign lesions in the pancreas, common bile duct, or periampullary area. Even though the mortality rate has dropped to almost 5% after pancreaticoduodenectomy, postoperative morbidity approaches 40% according to reports from several outstanding centers [22-27]. The most common complication is postoperative pancreatic fistula, which is closely associated with postoperative blood transfusion, with incidence rates ranging from 2.5% to 25% [28,29]. Recently, a randomized controlled study found that external drainage of the pancreatic juice reduced the incidence of postoperative pancreatic fistula [30]. Our group has developed a negative suction method for external drainage of pancreatic juice and also achieved successful results in patients undergoing pancreaticoduodenectomy for periampullary lesions and refusing to receive transfusions [31].

In addition to the surgical methods mentioned above, there are many new devices that can reduce blood loss and transfusion in HBP surgery. Like the Cavitron Ultrasonic Surgical Aspirator (CUSA), one of the most typical instruments, modern devices stimulate coagulation and permit faster transection of vessels; examples are the Harmonic scalpel, LigaSure (a bipolar vessel sealing device), Gyrus (a bipolar cautery device that causes adhesion to the hepatic parenchyma by combining pressure and energy to produce a mixture of elastin and collagen in the walls of the hepatic vessels and bile ducts), Aquamantys (an electrocautery technique that carries radiofrequency energy and saline concurrently to promote hemostatic adhesion and coagulation of soft tissue and bone in the operative field), and TissueLink Dissector [2,4,5,7]. However, there are other problems with them: thermal injury, increased risk of bile leak, and absence of conclusive evidence of efficacy and safeness. Therefore, further studies are needed to assess their efficacy and safety.

The influence of anesthesiologic technique on bleeding and transfusion rate in patients who have major HBP operations has to do mainly with intraoperative fluid management and the type of pharmacologic materials used. In addition to the low CVP strategy, several groups have developed the idea of lowering fluid volume not just by reducing fluid infusion but by phlebotomy [18].

Some pharmacologic procedures are useful for reducing or dealing with the complications of bleeding during HBP operations. Topical hemostatic materials can be categorized into three types: materials that mimic coagulation, materials that represent prototypes for endogenous coagulation, and integrated products that work as prototypes for endogenous and exogenous coagulation factors. There is some evidence that these approaches decrease coagulation time and the need for transfusions [2,7]. Antifibrinolytics can be divided into two categories: inhibitors of plasminogen (e.g. tranexamic acid) and inhibitors of plasmin (e.g. aprotinin). Recently, several studies have discussed the effectiveness and safety of antifibrinolytics in HBP surgery, especially in liver surgery and transplantation. However,

Table 2. New methods and materials for transfusion-free HBP surgery

Surgical	External drainage (e.g., pancreatic duct drainage)
	New instruments (e.g., Harmonic scalpel, LigaSure, Gyrus, Aquamantys, TissueLink)
Anesthesiologic	Intraoperative fluid management (e.g., fluid contraction)
Pharmacologic	Topical hemostatic agents
	Antifibrinolytics (e.g., Aprotinin, Tranexamic acid)
	Procoagulants (e.g., Recombinant factor VIIa)

even though antifibrinolytics have been widely studied in liver transplantation, only two studies have yielded positive results in patients undergoing hepatectomies. Thus, further studies of antifibrinolytics are required. The effectiveness and safety of recombinant factor VII have been examined in some randomized clinical studies in patients having major HPB surgery [32]. These studies did not uncover any major problems with safety, but they failed to show any decisive effect on bleeding or the need for transfusions.

The new methods and materials used in HBP surgery are listed in Table 2.

CONCLUSIONS AND PERSPECTIVE

An interdisciplinary multimodality approach to PBM results in good outcomes in HBP surgery. Increasing preoperative hemoglobin, using intraoperative blood-conservation methods and sophisticated procedures for reducing bleeding, and thorough care in the postoperative period, are the standards for patients who need blood management. Adhering to these standards should allow successful HPB surgery.

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