Pre-ICU

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Management of bleeding in visceral surgery and liver transplantation

The implementation of patient blood management programmes led to reduced blood product usage. However, haemorrhage secondary to major surgery remains a major cause of potentially preventable death. Considering the heterogeneity of procedures and technical approaches, it is not surprising that the bleeding risk stratification for visceral surgery is not clearly defined. However, there is agreement on the high bleeding risk of major hepatic surgery and liver transplantation. Massive bleeding protocols are also variable depending on local conditions: in some centres, the use of blood products in a fixed ratio is recommended, while in others a targeted approach using point-of-care guidance is favoured. In patients with liver dysfunction a restrictive fluid strategy and a targeted approach using factor concentrates guided by viscoelastic tests is recommended. We present a practical view on different aspects related to the management of bleeding in visceral and liver surgery.

I. Bleeding management in visceral and liver resection surgery

Preoperative assessment of bleeding risk is essential for adequate management of surgical patients. Bleeding risk depends both on the patient and the planned procedure. Regarding patient-related risk factors, congenital bleeding disorders are less common in the general population compared to acquired bleeding disorders such as antithrombotic therapy or associated pathology (liver or renal diseases, cancer, haematologic diseases). The bleeding risk stratification of visceral surgical procedures is not well established; except for cholecystectomy, hysterectomy and very short procedures, the other types of visceral surgical interventions are considered as high bleeding risk procedures similar to cardiac and orthopaedic surgery, based on definitions derived from anticoagulant bridging management studies (Spyropoulos and Douketis 2012). However, the high bleeding risk of major hepatic surgery and liver transplantation is recognised. In a study of more than 2000 patients with intraoperative bleeding exceeding 5 litres, the percentage of liver resection patients

included was higher than liver transplant or heart surgery patients (Irita 2011).

When preparing for high bleeding risk surgery, preoperative workup is essential. According to the European Society of Anaesthesiology (ESA) guidelines, the bleeding questionnaire is the best tool for assessing perioperative bleeding risk (Kozek-Langenecker et al. 2017). If preoperative anaemia exists, the causes must be identified and addressed, if possible (Kozek-Langenecker et al. 2017). Preoperative autologous donation is a technique useful in patients with extremely rare blood groups or with multiple antibodies (Vassallo et al. 2015). It decreases the incidence of allogenic blood transfusion, but actually increases the overall incidence of transfusion because of the lower preoperative haemoglobin levels compared to patients who did not pre-donate blood (Vassallo et al. 2015; Henry et al. 2002).

In order to decrease intraoperative blood loss, the prevention of hypothermia, hypocalcaemia and acidosis is extremely important (Martini 2009; Kozek-Langenecker et al. 2017). Deliberate induced hypotension was associ-

ated with a significant reduction in operative blood loss in patients undergoing orthopaedic or neurosurgical procedures (Soghomonyan et al. 2017; McNeill et al. 1974). However, this strategy needs an individualised approach to balance the risks of blood loss with the preservation of vital organ perfusion. Other autologous blood conservation techniques used in visceral surgery include acute normovolaemic haemodilution (ANH) and cell salvage. ESA guidelines recommend against the use of controlled hypotension combined with ANH and caution when using ANH in patients with preexistent coagulopathy (Kozek-Langenecker et al. 2017). Intraoperative cell salvage reduces the need for allogenic blood transfusions and it is often used in cardiac and orthopaedic procedures. In abdominal surgery, the use of intraoperative cell salvage is lower due to concerns about the risks of reinfusing malignant cells (in oncologic patients) or infection risk (in bowel surgery). However, the use of cell salvage is not contraindicated in oncologic patients or in bowel surgery, provided adequate precautions are undertaken (Kozek-Langenecker et al. 2017).

Visceral surgery

In some situations, the occurrence of life-threatening bleeding during visceral surgery cannot be avoided and adequate measures are essential for a successful outcome. In the event of a massive bleeding situation, the three key elements of blood volume replacement, optimisation of tissue oxygenation and coagulopathy prevention must be remembered. The activation of a massive bleeding protocol with intervention algorithms adapted to local conditions is highly recommended (Kozek-Langenecker et al. 2017). There are several types of massive transfusion protocols. In some centres the massive transfusion protocol recommends administration of red blood cells (RBC), fresh frozen plasma (FFP) and platelet concentrate in a specified ratio according to local guidelines. The use of ratio-based resuscitation was extended beyond the trauma setting, but we still lack studies demonstrating its benefits in non-trauma patients(Mesar et al. 2017). Additional studies are required to define the optimal ratios in different types of surgical patients (Mesar et al. 2017). In some centres the massive transfusion protocol recommends a targeted approach for bleeding patients using point-of-care-based algorithms. Another option to address massive bleeding is a combination of massive transfusion protocols: initiation of a ratio-driven transfusion protocol from start of haemorrhage with an early shift towards a targeted approach when the situation allows timely results of point-of-care or standard coagulation tests (Johansson et al. 2014; Ghadimi et al. 2016). Recently a further option for treating massive bleeding based on the essential role of fibrinogen in the coagulation process was described in trauma patients, recommending the administration of fibrinogen concentrate and RBC in a manner similar to the 1:1 ratio (Rossaint et al. 2016).

Regardless of the massive bleeding protocol used, the final goal is to decrease patient morbidity and mortality. In a study aiming to identify a haemoglobin target associated with the least odds of death after resuscitation has been completed and the patient's vascular space has equilibrated, it was demonstrated that both over-transfusion and under-transfusion were associated with increased mortality (Zielinski et al. 2016).

Liver resections

Liver resections have been associated with high mortality and morbidity rates. In a review published in 2007, de Boer et al. underlined the effect of blood loss and blood transfusions in liver surgery and the relevant association between blood transfusion and postoperative morbidity, especially infectious complications (de Boer et al. 2007). A decade on, blood transfusion continues to be an independent predictor of mortality and morbidity in patients undergoing major or minor hepatectomy, both for benign and malignant pathology.

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Reducing blood loss and blood transfusions in liver surgery is mandatory for improving patients' outcome. As bleeding usually occurs during liver parenchymal transection, the control methods used by surgeons include vessel occlusion techniques and the use of different instruments for resection (Romano et al. 2012). There are several techniques of hepatic vascular control methods, but the main ones are the inflow vascular occlusion of the liver (known as Pringle's manoeuvre with the occlusion of the triad within the hepatoduodenal ligament) and total hepatic vascular exclusion (THVE) (the combined inflow and outflow vascular occlusion) (Romano et al. 2012; Huntington et al. 2014). Anaesthetic management is adapted to the technique used for the reduction of operative bleeding. When inflow vascular occlusion of the liver is applied, maintenance of a low central venous pressure (CVP) is recommended in order to decrease blood loss (Li et al. 2014; Huntington et al. 2014; Kozek-Langenecker et al. 2017; Moggia et al. 2016). Potential risks of this technique are inadequate vital organ perfusion, air embolism and loss of volaemic reserve in case of bleeding (Huntington et al. 2014). The methods for maintaining a low CVP include intravenous fluid restriction, systemic nitroglycerin, furosemide, intravenous

morphine and even intraoperative whole blood phlebotomy, but an individualised strategy is recommended for obtaining a low CVP while minimising the associated risks (Huntington et al. 2014; Rekman et al. 2017; Tympa et al. 2012). The use of the low CVP approach is not associated with intraoperative blood loss reduction during hepatic resections in healthy donors for living related liver transplantation (Kim et al. 2009; Choi et al. 2015). The low CVP technique is abandoned in the case of massive bleeding or in cases when the inflow vascular occlusion technique is converted to THVE (Romano et al. 2012).

While Pringle's manoeuvre is generally associated with haemodynamic stability, with a small decrease in cardiac output, and increase in systemic vascular resistance and mean arterial pressure, in THVE rapid haemodynamic changes are expected due to caval clamping, blood loss or hepatic reperfusion (Tympa et al. 2012). Selective hepatic vascular exclusion has a haemodynamic profile similar to inflow vascular occlusion techniques. It provides a bloodless surgical field and it is indicated when CVP cannot be lowered despite adequate management. It is tolerated by most patients and it is more effective than Pringle's alone in controlling bleeding (Tympa et al. 2012).

II. Bleeding management in liver surgery for patients with chronic liver disease

An increasing number of patients with chronic liver diseases are scheduled for non-transplant surgery. For abdominal surgery, the perioperative mortality of cirrhotic patients is correlated with the severity of the liver disease as assessed by the Child-Pugh or Model for End-Stage Liver Disease (MELD) scores (Lopez-Delgado et al. 2016). Historically, patients with liver cirrhosis were considered to be at risk of bleeding due to coagulation defects; however, according to more recent research, bleeding in cirrhosis is due mainly to vascular abnormalities (Tripodi and Mannucci 2011). In health, there is a balance between pro- and anti-haemostatic factors. In compensated cirrhosis, this balance is maintained, the anti-haemostatic factors being counterbalanced by pro-haemostatic factors (Tripodi and Mannucci 2011). The prolongation of standard coagulation tests (Activated Partial

Thromboplastin Time [aPTT], Prothrombin Time [PT], International Normalised Ratio [INR]) in cirrhotic patients reflects only the deficit in pro-coagulant factors, being insensitive to the concomitant decrease in anticoagulants (Tripodi and Mannucci 2011). In vitro studies demonstrated similar amounts of thrombin generated in cirrhotic patients as in healthy controls when using a thrombin generation assay modified to reflect the action of both pro-coagulants and anticoagulants (Tripodi et al. 2005). Not only is the plasmatic coagulation rebalanced in cirrhosis, but also the primary haemostasis where the low number of platelets is compensated by the increased plasmatic levels of von Willebrand factor leading to increased platelet adhesion capacity (Lisman et al. 2006). The balance of fibrinolysis is also maintained by concomitant alterations of pro- and anti-fibrinolytic factors and by clot structure changes associated with decreased clot permeability and increased resistance to lysis (Hugenholtz et al. 2016; Lisman et al. 2001). However, this rebalanced haemostatic system in cirrhosis is not as stable as in health and can be easily disturbed by different precipitating events (Tapper et al. 2013; Saner et al. 2013). As a result, bleeding management in cirrhotic patients undergoing surgery has to preserve this fragile balance for as long as possible. As prolonged standard coagulation tests are not useful to reflect the rebalanced haemostasis in cirrhosis, it is not recommended to correct them before invasive procedures, but rather to limit haemostatic interventions to bleeding patients (Saner et al. 2013). The administration of FFP determines volume loading, with increased portal and venous pressure correlated with increased surgical bleeding. Therefore a restrictive fluid approach and targeted therapy with factor concentrates guided by viscoelastic point-of-care tests in bleeding patients are recommended (Saner et al. 2013; Kozek-Langenecker et al. 2017). In cirrhotic patients undergoing liver resections the use of antifibrinolytic drugs should also be considered (Kozek-Langenecker et al. 2017).

Liver transplantation

The same principles are applied in cirrhotic patients undergoing liver transplantation (LT). During liver transplant surgery, there are specific recommendations for the different surgical phases:

i) In the first stage of LT the dissection and mobilisation of the liver may lead to significant surgical bleeding, especially in patients with abdominal adhesions or increased portal pressure (Görlinger et al. 2016). The use of cell salvage techniques, a low CVP strategy and a targeted approach guided by viscoelastic tests for bleeding management are recommended (Görlinger et al. 2016; Kozek-Langenecker et al. 2017).

ii) During the anhepatic phase, surgical bleeding is uncommon as all the major vessels are clamped and bleeding is usually due to coagulopathy. Due to the increased release of tissue plasminogen activator (tPA) from endothelial cells and the absence of hepatic clearance function, hyperfibrinolysis can occur in this phase (Görlinger et al. 2016).

iii) The last phase of the LT procedure, the neohepatic phase, begins with the reperfusion of the graft and is characterised by profound haemostatic abnormalities leading in some cases to clinically important bleeding. Hypothermia, acidosis and hypocalcaemia are frequently encountered after reperfusion contributing to the worsening coagulopathy (Görlinger et al. 2016). Thrombocytopaenia is aggravated as platelets get trapped in the graft; due to the tPA release from the graft, hyperfibrinolysis is common after reperfusion. However, in most cases it is self-limited (Görlinger et al. 2016). A heparin effect can occur in the neohepatic phase due to the release from the graft of the exogenous heparin administered to the donor before aortic cross-clamping and of the endogenous heparin-like substances from endothelial cells (Görlinger et al. 2016). With a functional liver graft, the hyperfibrinolysis and the heparin effect are self-limited and treatment is not necessary in the absence of diffuse bleeding (Görlinger et al. 2016).

The algorithms for bleeding management in liver transplant surgery include predefined trigger and target values usually based on viscoelastic testing and recommend haemostatic interventions only in bleeding patients and not for correction of abnormal test results. A sequential approach is recommended, addressing first hyperfibrinolysis, then clot firmness, followed by the correction of enzymatic factors deficiency (Görlinger et al. 2016). Due to the antithrombin deficiency in cirrhosis and the low antithrombin content of prothrombin complex concentrates (PCC), it seems that a lower dose of PCC compared to the dose required for warfarin reversal is enough for restoring reduced thrombin generation in cirrhotic patients undergoing liver transplant surgery (Abuelkasem et al. 2017).

Caution is recommended when procoagulant therapy is administered in cirrhotic patients, as the balance of haemostasis can easily tip toward thrombosis. Bleeding is a major concern during LT, but the overzealous replacement of deficient procoagulant factors should be avoided, as intraoperative thrombotic events such as intracardiac thrombosis or pulmonary embolism are often fatal (Feltracco et al. 2015; Warnaar et al. 2008). In the early postoperative period, hepatic vessel thrombosis is a threat to both patient and graft survival and prophylactic antithrombotic treatment must be considered despite hypocoagulable routine laboratory tests (Arshad et al. 2013).

Conclusion

Bleeding management in visceral surgery and liver transplantation is extremely complex and requires a comprehensive perioperative coagulation treatment algorithm adapted to the local conditions of each institution as a backbone for the construction of an individualised treatment plan adapted to each patient.

Conflict of interest

Ecaterina Scarlatescu declares that she has no conflict of interest. Dana R. Tomescu declares that she has no conflict of interest. ∎

Abbreviations
ANH acute normovolaemic haemodilution
CVP Central venous pressure
FFP fresh frozen plasma
LT liver transplantation
RBC red blood cells
THVE Total hepatic vascular exclusion

References
For full references, please email editorial@icu-management. org or visit https://iii.hm/k6w