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REVIEW
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Hemostasis in liver surgery: Indonesian Society of Digestive Surgeons (IKABDI) consensus statements

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ABSTRACT

Liver resection is a complex operation with bleeding control as one of the most crucial factors. It is essential to determine the amount of bleeding to predict the mortality and morbidity after liver surgery. With technology and scientific development, liver resection can use open or laparoscopic surgical techniques supported by various energy devices and medical management. However, the main goal is to remove the tumor with adequate negative margins and good flow. Indonesian Society of Digestive Surgeons agreed to have an agreement using the Modified Delphi method consisting of twenty digestive surgeons. The consensus was established for hemostasis management choices as surgical and medical strategies in liver surgery. The surgical strategies recommendation include performing anatomical resection in primary hepatic tumor and non-anatomical resection for liver metastases; using of Glissonean Pedicle approach as an inflow control option; doing routine intermittent pringle maneuvers; prohibiting total vascular exclusion; and making a statement that no particular energy device preferred for transecting the liver parenchyma. For medical strategies, consensus recommends limiting the transfusion of PRC or any other blood components, antifibrinolytic's role as hemostatic agents, and using fibrin sealant and matrix coagulant sheets for hemostatic agents in liver surgery. These recommendations reflect current knowledge and can be reviewed if new findings are discovered. Hopefully, this consensus can be a valuable guide for surgeons, especially those practicing in Indonesia, to provide low mortality and morbidity in liver resection.

Keywords: Bleeding control, Liver resection, Medical Strategy, Surgical Strategy.
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INTRODUCTION

Liver resection is a complex operation and a process that has continued to evolve since Lortat-Jacob first described it in 1952 when they reported the first anatomical right hepatectomy for liver cancer.[1] The amount of bleeding is an essential determinant of mortality and morbidity from liver resection surgery. Therefore, bleeding control is a crucial part of liver resection. In general, significant bleeding in liver resection occurs in 3 phases. The first phase is the process of mobilization of the liver, especially in tumors with a large size, located posteriorly, close to the right or middle hepatic vein, and attached to the diaphragm or retrohepatic vena cava. The second phase is parenchyma resection, especially when the parenchyma is in a fragile, steatotic, or cirrhotic state, which is also exacerbated by distortion of the intrahepatic veins due to the existing tumor. The third phase occurs when there is parenchyma bleeding at the margins of the resection. In conclusion, parenchymal resection is the most challenging stage and carries a high risk of bleeding, which is the crucial prognostic variable of liver resection surgery results.[2–4]

Therefore the process of hemostasis in surgery on the liver is a topic of particular concern. With the development of technology and science, the liver resection process has been carried out using open or laparoscopic surgical techniques, supported by various energy devices and medical management, both intravenous and topical hemostatic agents. All developments stay close to the primary goal of ensuring hemostasis without sacrificing the aims and objectives of surgery on the liver, namely "removing the tumor with adequate negative oncological margins, ensuring adequate biliary drainage, arterial

inflow, and venous outflow". Jarnagin et al. concluded that with the development of surgical techniques and advancements in operating technology in the "energy devices," experienced liver surgeons can reduce morbidity and mortality from liver resection operations by up to 3% - 5%. Experienced hepatobiliary centers can even achieve a mortality of less than 3%.[5] These results are similar to studies from other centers, which reported mortality from perioperative liver resection of 2.6% - 8.4%. Lee et al. supported these findings with mortality data at 30 days after surgery of 1.8% and mortality during hospitalization by 2.9%.[6–10]

This article will further discuss the principles of surgical techniques such as anatomical or non-anatomical resection, inflow control in the glissonean pedicle approach, the pringle maneuver, and the energy devices used to reduce the risk and amount of bleeding in liver surgery. The use of pro-coagulant medications, topical hemostasis agents, and blood components will also be discussed concerning their benefits for reducing the risk of bleeding. The author hopes that discussing the above factors can be a valuable guide for surgeons interested in performing surgical procedures on the liver to provide results with low mortality and morbidity.

METHOD

We gathered an expert panel to generate relevant literature, discuss new findings, and answer some clinical questions through the voting process. All questions are elaborated into statements that were answered through the Likert scale to conclude specific opinions that might direct management choices for controlling hemostasis in liver surgery. All panelists were encouraged to think based on the latest literature and include their self-opinions also practice preferences.

Twenty panelists who came to the consensus meeting were selected as Hepato- Pacreatico-Biliary surgery experts. All the experts are fellowship-trained via programs accredited by the Indonesian Society of Digestive Surgeons (KIBDI) with other diverse medical and surgical training experiences. Some expert panel members were asked to give short lectures on the conference day.

RESULTS

IKABDI Consensus Agreements

Surgical strategy for hemostasis in liver surgery

IKABDI recommends:

1. Perform anatomical resection compared to non-anatomical resection for HCC. For secondary hepatic tumors or liver metastases from colorectal cancer, non-anatomical liver resection is still acceptable. (55%, 11/20)
2. Inflow control with the Glissonean Pedicle approach compared to individual ligation (75%, 15/20)
3. Do intermittent pringle maneuvers as routine compared to changes between continuous or intermittent maneuvers. (55%, 11/20)
4. Not performing total vascular exclusion in liver surgery. (50%, 10/20)
5. There is no special energy device preferred for transecting liver parenchyma. Chosen of an energy device depends on the availability of energy device facilities in each health facility. In this survey, most surgeons use the ultrasonic device. (55%,11/20)

Medical strategy for hemostasis in liver surgery

IKABDI recommends:

1. Limit the use of PRC transfusion for medical hemostasis strategies in liver surgery. (80%, 16/20)
2. Limit the administration of blood component transfusions (fresh frozen plasma, thrombocyte concentrate, and cryoprecipitate) for medical hemostasis strategy in liver surgery. (95%, 19/20)
3. Antifibrinolytics as the chosen pharmacological hemostatic agents in liver surgery. (95%, 19/20)
4. Fibrin sealant (75%, 15/20) and matrix coagulant sheets (95%, 19/20) as topical hemostatic agents in liver surgery.

DISCUSSION

Surgical strategy for hemostasis in liver surgery

Anatomical vs. Non-anatomical Surgery for Hepatocellular Carcinoma and secondary liver tumors

Solitary HCC patients who undergo anatomical or non-anatomical surgery still have a controversial long-term survival. The survival rate is strongly influenced by the recurrence of HCC, which is determined based on the unique nature of the tumor. Hepatocellular carcinoma has intrahepatic metastases capability by following the pattern of the portal vein branches. Liver surgery is expected to minimize the recurrence possibility.[11] Hu Liu et al. showed that anatomical liver surgery has better disease-free survival outcomes in HCC cases. Anatomical surgery removes the primary tumor along with its microvascular metastases.[12]

Whereas in secondary liver tumors, the mainly discussed is metastases from colorectal cancer, having a different surgical strategy for the liver. Traditionally, anatomical surgery was recommended for liver metastases that invaded the major portal pedicle or hepatic vein, but with current scientific developments, the use of anatomical surgery for small, oligometastatic, and even large, multifocal nodules is increasingly being questioned.[13,14] Therefore, parenchymal sparing hepatectomy (PSH) was emerging for secondary/metastatic tumors in the liver. Moris et al. conducted a meta-analysis of 12 studies with 2500 patients. They found that PSH did not differ significantly from anatomical surgery in terms of long perioperative mortality, length of stay, the incidence of recurrence of tumors in the liver, length of tumor-free resection margins, and long-term survival of patients with liver metastases due to colorectal cancer.[15–17] Anatomical procedure has a greater risk of liver failure than PSH because PSH results in greater future liver remnants.[16]

In this IKABDI consensus, 55% of experts prefer anatomical surgery for primary HCC cases, but in liver metastases or secondary tumors cases, non-anatomical surgery or PSH is acceptable.

Inflow control

As mentioned, bleeding volume during liver surgery is crucial for determining the operation outcome. Inflow control is one of the effective ways to control bleeding; there are two main techniques in inflow control, namely the *glissonean pedicle approach* (extrafascial) and the intrafascial hilar approach. Both techniques are

part of selective inflow clamping, which differs from portal triad clamping (PTC) or the Pringle maneuver. Rahbari et al. conducted a meta-analysis study of 8 randomized controlled trials (RCT) consisting of 558 patients, showing that intermittent PTC compared to no PTC did not provide a significant difference, as well as when combined with ischemic preconditioning (IPC). It is just that the levels of alanine transferase (ALT) are lower in patients who do PTC with a combination of IPC.[18]

Pringle's maneuver role in liver surgery

Pringle's maneuver, also known as PTC, is one of the oldest methods controlling the inflow of blood vessels into the liver, but it cannot control backflow originating from the hepatic veins.[19] There are several alternative ways of doing the pringle's maneuver, namely: continuous and intermittent pringle's maneuver, which can be done routinely or not. In this consensus, as much as 55% chose to do the intermittent pringle maneuver routinely. The consensus is that the use of the intermittent pringle maneuver is agreed upon for 15 minutes of ischemia followed by a 5-minute reperfusion period, with the period above proven not to cause substantial injury to the liver parenchyma, with a maximum ischemic time limit of 120 minutes before causing damage to the liver parenchyma.[18,20] Santigo et al. demonstrated the safety of the intermittent pringle's maneuver in minimally invasive liver resection of KHS patients with cirrhotic liver conditions, as assessed by the absence of significant changes in serum liver function.[21]

In several other studies, the intermittent pringle's maneuver was considered to lose its role because it was considered not significantly different in terms of the amount of bleeding, morbidity, and mortality after liver resection when compared to the group that did not perform the intermittent pringle's maneuver or the continuous pringle's maneuver followed by ischemic preconditioning.[18,20–22]

Total vascular exclusion in liver surgery

With Pringle's maneuver, total vascular exclusion completely stops blood flow to the liver by placing a clamp on the infra- and supra-hepatic inferior vena cava. The primary function of total vascular exclusion is to reduce the bleeding risk upon transecting the liver parenchyma. On the other hand, it is indicated for liver tumors adjacent to/infiltrating the vena cava and confluent of the hepatic veins, although this maneuver can result in significant hemodynamic compromise.[23,24]

Selective hepatic vascular exclusion (SHVE) is a clamping procedure of the hepatic vein and inflow to the portal triad ipsilaterally with the liver parenchyma to be respected without clamping the inferior vena cava (IVC). This procedure is especially indicated for tumors at the hepatic veins confluence, which can reduce the degree of mortality, the amount of bleeding, the amount of blood transfused, air embolism, liver failure, and multiple organ failure. On the other hand, the technique can cause lacerations of the hepatic veins and lead to major bleeding, with does not make a significant difference in statistics in terms of postoperative bleeding, operating time, warm ischemia time, and time of hospitalization, and stay in the ICU.[25–27]

Regarding all the studies above, this consensus does not recommend total vascular exclusion, and there is no specific consensus regarding the SHVE procedure.

Energy device in liver surgery

Until now, there is limited evidence to recommend the best surgery tool or energy device for liver parenchyma transection.[28] Several studies have explained that the clamp-crushing technique is a choice in elective liver parenchymal transection because fast and associated with less bleeding.[29,30]

Kamarajah et al. explained that bipolar cautery was the best at reducing bleeding risk with the shortest operating time, while the harmonic scalpel was considered the best at reducing the risk of post-major surgery and the need for transfusions.[31]

Medical strategy for hemostasis in liver surgery

Packed red cells transfusion in liver surgery

Intra- and postoperative PRC transfusions have been reported to have a significant association with adverse outcomes of liver resection surgery compared to patients who did not receive them.[32,33] It was found to be an intraoperative predictor for postoperative complications of liver resection with the highest odds ratio (OR 17.1).[32] Patients with HCC who underwent resection and received PRC transfusions showed lower overall survival (OS), disease-free survival (DFS), and recurrence within five years than those who did not receive transfusions.[33,34] Those who received perioperative PRC transfusions had a hazard ratio (HR) of 2.43 (1.90–3.15 95%CI) for OS and 1.46–2.84 for DFS and an OR of 1.42 (1.20–1.67, 95%CI) for five-year recurrence rate. Although it has shown a significant association with adverse outcomes, there is still controversy regarding the relationship between perioperative PRC transfusion and mortality after liver resection surgery.[33]

Administration of PRC transfusions, especially allogeneic and non-leucodepleted, has an immunomodulatory effect on recipients causing susceptibility to infection and interfering with anti-tumor immunological activity.[33,35] This reason is the underlying cause of negative (complication rates, OS, DFS, recurrence) postoperative liver resection outcomes of patients. Postoperative infection is the most common complication or morbidity caused by the immunomodulatory effect. The immune effect causes a decrease natural killer (NK) cell function, the helper-to-suppressor T lymphocyte ratio, the efficacy of antigen presentation, tolerance for some tumor antigens, and the hematopoiesis system suppression.[35] Procter et al. added that serum depletion of extracellular arginine, an essential amino acid for immunity, is a mechanism of the immunosuppressive effect of PRC. It has been speculated that components of growth factors (vascular endothelial growth factor, transforming growth factor-B) in PRC and increased inflammato response due to immunomodulation stimulate the spread and proliferation of cancer cells.[34] However, the underlying mechanism for adverse oncology outcomes (recurrence, DFS) is still uncertain.[35] On the other hand, autotransfusion studies using intraoperative blood salvage techniques and leuko-depleted transfusions reported

no effect on OS or DFS outcomes in patients with liver carcinoma who underwent resection or transplantation.[36]

With the uneven health services quality distribution, the current consensus limits the use of PRC transfusion for liver resection surgery. Efforts to improve the quality of health services continue to provide services with the latest evidence findings.

Limitation of PRC transfusions carried out by implementing patient blood management protocols by each institution's policies. We recommend considering PRC transfusion when[35]

- Post-hepatectomy Hb < 7.5 mg/dL
- Hemodynamically stable patients with Hb < 7.0 mg/dL in the late postoperative period
- Patients with coronary heart disease and Hb < 8.0 mg/dL in the late postoperative period

There is a management protocol that is commonly used, namely the Ottawa criteria for appropriate transfusion in hepatectomy (OCATH), and can be applied in clinical services as follows,[37]

- Intraoperative
- It is never inappropriate to transfuse with reason,
- Significant bleeding (>1500 mL) and ST segment changes
- Hb < 7.5 mg/dL
- Transfusion in conditions of Hb > 9.5 mg/dL is not permitted if there is no severe condition (bleeding > 1500 ml, ST segment changes)
- Transfusion in Hb > 8.5 mg/dL must have strong justification.
- Postoperative
- In stable (asymptomatic) patients, there is Hb < 7.0 mg/dL (without CHD) or Hb < 8.0 mg/dL (with CHD).
- If a decrease in Hb > 1.5 mg/dL, it is appropriate to do a transfusion when Hb < 7.5 mg/dL

Blood components transfusion in liver surgery

As discussed in the previous sub-points, allogeneic blood administration has potential adverse effects and is associated with negative postoperative outcomes. Limited studies address the correlation between blood component transfusions and the postoperative outcome of liver resection. Bednarsch et al. reported that intraoperative administration of FFP was a significant independent predictor (HR: 6.52, p: 0.001) of perioperative morbidity in patients undergoing partial hepatectomy for liver carcinoma.[38] Therefore, giving blood component transfusions also needs to consider the possible advantages and risks.

Plasma transfusion (FFP) is indicated in patients with bleeding coagulopathy or an INR > 2.0. In addition, FFP transfusion is also indicated for urgent warfarin reversal or anticipating invasive procedures that have a significant bleeding risk with an INR > 1.5. Administering vitamin K for urgent warfarin reversal is necessary to reduce the need for FFP transfusions.[39]

Platelet transfusion is required in patients undergoing liver resection procedures with a platelet count <50,000 with signs of bleeding. In addition, platelet administration is used to anticipate invasive procedures with a high risk of bleeding. Platelet transfusion is not indicated in surgical patients with normal platelet function and a platelet count > 100,000. Platelet transfusion should be considered when a large number of PRC transfusions are performed, and it is uncommon to check the platelet count. Cryoprecipitate is given for uremic bleeding or has a serum fibrinogen concentration of <100 mg/dL accompanied by coagulopathic bleeding. Cryoprecipitate transfusion is rarely indicated at fibrinogen concentrations >150 mg/dL.[39]

Given the need to reduce the risk of intraoperative bleeding affecting patient outcomes, the consensus recommends blood component transfusions (FFP, TC) in liver resection surgery.

Pharmacological hemostatic agents uses in liver surgery

Antifibrinolytics administration can reduce bleeding and the need for blood transfusions intraoperatively in liver surgery (resection, transplant). During liver resection, a patient will occur impaired liver synthesis function that causes coagulopathy and impaired hemostasis. The direct liver resection injury will cause a systemic inflammatory effect that exacerbates the state of hemostasis. This pathophysiology underlies the secondary effects of hemodilution, hypothermia, and acidosis, leading to hyperfibrinolysis and excessive bleeding risk.[40,41]

Administration of antifibrinolytic agents, including plasmin inhibitors (aprotinin) and plasminogen inhibitors (tranexamic acid (TXA)), has been reported to inhibit hyperfibrinolysis. On the other hand, aprotinin is more effective in reducing bleeding but increases mortality rates and renal impairment compared to TXA.[41] Whereas TXA reduced the need for blood transfusions (OR 0.09; 95% CI 0.01 to 0.72; p 0.02) and was safe to use with no difference in thromboembolic events and mortality rates.[40] Although the mechanism of action of TXA is known by inhibiting plasminogen, thereby reducing the occurrence of fibrinolysis, a study by Karanicolas et al. reported no differences in INR, PTT, fibrinogen, and plasmin-antiplasmin parameters compared to the control group (not given TXA). This finding suggests that TXA may have a different mechanism than bleeding in other organs to reduce bleeding from liver surgery.[41]

Therefore, the current consensus is that tranexamic acid is the preferred antifibrinolytic agent for reducing intraoperative bleeding.

Topical hemostatic agents uses in liver surgery

Topical hemostatic agents have been shown to help surgeons control intraoperative bleeding by accelerating hemostasis time (MD −2.33 minutes; 95% CI [−3.52, −1.15]; p 0.0001).[42] There are several topical hemostatic agents, such as fibrin sealants and matrix coagulants, are proven and can be an option for controlling bleeding in liver surgery.[43] Fibrin sealant was reported to accelerate the time to hemostasis (MD −208.46; 95% CI [−228.22, −188.70]; p 0.0001) and increase the success of hemostasis (RR 1.35; 95% CI [1.17, 1.57]; p 0.0001) compared to the control group (coagulant matrix agent).[44]

Fibrin sealant as a hemostatic agent contains human plasma protein fraction consisting of two main components (fibrinogen and thrombin) that reduce the risk of hypersensitivity reactions and are non-toxic and safe to use.[45] Fibrin

sealant mechanism reproduces the end stages of the physiological coagulation cascade and forms a stable fibrin clot that can help achieve hemostasis.[46] The meta-analytic study by Well et al. demonstrated that the fibrin sealant method was superior (OR 9.69; 95% CI [3.67–33.51]) over other methods for accelerating hemostasis in liver resection surgery.[43] In addition to fibrin sealants, coagulant matrix hemostatic agents can also help control bleeding in liver resection surgery physically and biologically. Physical polymeric agents such as cellulose, gelatin, or collagen form a coagulant matrix at the bleeding site that activates the extrinsic coagulation cascade and serves as an initial step for clot formation. The use of a coagulant matrix helps surgeons to manage intraoperative bleeding. The combined use of fibrin sealant and matrix coagulant together showed a shorter time to achieve hemostasis (MD −2.33 min; 95% CI [-3.52, −1.15]; p 0.0001) than the use of a single hemostatic agent.[42]

In conclusion, this current consensus favors using topical hemostatic agents such as fibrin sealants only or in conjunction with matrix coagulant sheets (cellulose, gelatin, collagen) to manage intraoperative bleeding.

CONCLUSION

The current recommends surgical and medical strategies for control bleeding in liver surgery. Anatomical resection technique recommended in primary hepatic tumor and non-anatomical resection for liver metastases. Glissonean Pedicle approach is preferred as an inflow control option and it is recommended to perform routine intermittent pringle maneuvers. Consensus prohibited total vascular exclusion and made a statement that no superior energy device for transecting liver parenchyma. It is recommended to limit PRC and other blood components transfusion during operation. In order to reach hemostasis in liver surgery, we can use antifibrinolytic, fibrin sealant, and matrix coagulant sheets.

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AUTHOR CONTRIBUTION

All authors have contributed to this research process, including conception and design, literature search, clinical studies, data analysis, interpretation of the data, drafting of the article, critical revision of the article for important intellectual content, final approval of the article, and collection and assembly of data.

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