Optimizing Risk Stratification in Portal Vein Thrombosis after Splenectomy and its Primary Prophylaxis with Antithrombin III Concentrates and Danaparoid Sodium in Liver Cirrhosis with Portal Hypertension

Hirofumi Kawanaka, MD, PhD, Tomohiko Akahoshi, MD, PhD, Shinji Itoh, MD, PhD, Tomohiro Iguchi, MD, PhD, Norifumi Harimoto, MD, PhD, Hideaki Uchiyama, MD, PhD, FACS, Tomoharu Yoshizumi, MD, PhD, FACS, Ken Shirabe, MD, PhD, Kenji Takenaka, MD, PhD, Yoshihiko Maehara, MD, PhD, FACS

BACKGROUND: Decreased antithrombin III (ATIII) activity and large splenic vein diameter (SVD) are risk factors for portal vein thrombosis (PVT) after splenectomy in liver cirrhosis with portal hypertension. Antithrombin III concentrates can prevent PVT. This study was designed to stratify risks for PVT after splenectomy in cirrhotic patients and to develop prophylactic protocols for PVT.

STUDY DESIGN: In 53 patients (testing cohort), the cutoff level of preoperative ATIII activity ($\leq$60%) was evaluated for administration of ATIII concentrates. Antithrombin III activity and SVD were re-evaluated as criteria for prophylaxis of PVT. In 57 patients (validation cohort), the risk stratification of PVT and prophylactic protocols were validated.

RESULTS: In the testing cohort, 10 (19%) of 53 patients had PVT. Risk level of PVT was stratified and prophylactic protocols were developed. Patients at low risk (ATIII activity $\geq$70% and SVD $<$10 mm) were not treated; those at high risk (ATIII activity $<$70% or SVD $\geq$10 mm) received ATIII concentrates (1,500 U/day) for 3 days; and those at highest risk (SVD $\geq$15 mm) received ATIII concentrates for 3 days, followed by danaparoid sodium (2,500 U/day) for 14 days and warfarin. In the validation cohort, 0 of 14 low-risk and 2 of 32 high-risk patients had PVT. Although 8 of 11 patients at highest risk had temporary PVT, it disappeared within 3 months postoperatively. Finally, only 2 (3.5%) of 57 patients had PVT.

CONCLUSIONS: Risk stratification of PVT after splenectomy and prophylaxis with ATIII concentrates and danaparoid sodium dramatically reduced the incidence of PVT. (J Am Coll Surg 2014; 219:865–874. © 2014 by the American College of Surgeons)

Recent technical advances in laparoscopic surgery have enabled safer and less-invasive laparoscopic splenectomy, even in patients with liver cirrhosis and portal hypertension.[1] The evolution of treatments for chronic liver diseases, such as interferon (IFN) therapy for hepatitis C virus (HCV), has shed light on laparoscopic splenectomy for liver cirrhosis and hypersplenism.[2] Currently, splenectomy is performed to improve thrombocytopenia before the start of IFN therapy for HCV infection[3] and during treatment for hepatocellular carcinoma.[4] Splenectomy is also performed concurrently with living donor liver transplantation to reduce graft congestion and after living donor liver transplantation to alleviate persistent portal hypertension and thrombocytopenia.[5,6] Although portal vein thrombosis (PVT) is not a rare complication of splenectomy and can be fatal in patients with liver cirrhosis, it remains to be resolved. It is important to determine risk factors for PVT and to prevent PVT after splenectomy in cirrhotic patients.

Disclosure Information: Nothing to disclose.

Received May 24, 2014; Revised July 21, 2014; Accepted July 30, 2014.

From the Departments of Surgery and Multidisciplinary Treatment (Kawanaka, Iguchi, Maehara) and Surgery and Science (Kawanaka, Akahoshi, Itoh, Iguchi, Harimoto, Yoshizumi, Shirabe, Maehara), Graduate School of Medical Sciences, Kyushu University and Department of Surgery, Fukuoka City Hospital (Uchiyama, Takenaka), Fukuoka, Japan.

Correspondence address: Hirofumi Kawanaka, MD, PhD, Department of Surgery and Multidisciplinary Treatment, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan. email: harrykw@v102.vaio.ne.jp

http://dx.doi.org/10.1016/j.jamcollsurg.2014.07.939
ISSN 1072-7515/14

Abbreviations and Acronyms

ATIII = antithrombin III
HCV = hepatitis C virus
IFN = interferon
LMWH = low-molecular weight heparin
POD = postoperative day
PVT = portal vein thrombosis
ROC = receiver operating characteristic
SVD = splenic vein diameter
UFH = unfractionated heparin
US = ultrasonography

Bleeding complications, such as esophageal variceal hemorrhage, are frequent in patients with liver cirrhosis. These patients are considered to be in a state of auto-anticoagulation, accompanied by prolonged prothrombin time and INR, as well as thrombocytopenia.[7] Hemostatic systems in patients with liver cirrhosis are delicately balanced between pro- and anticoagulant factors and can be easily tipped to a hypo- or hypercoagulable status, resulting from decreased levels of procoagulant and anticoagulant factors synthesized by hepatocytes and sinusoidal cells.[7-9] Hypercoagulability has an underestimated but crucial role in many aspects of liver cirrhosis. Thrombin generation, as a more balanced marker of coagulation status, is normal, despite the abnormal prothrombin time and INR.[10-12] Reduced production of anticoagulants, such as protein C, protein S, and antithrombin III (ATIII), coupled with the increased production of the procoagulants factor VIII and von Willebrand factor, put cirrhotic patients at increased risk for hypercoagulopathy.[8,13,14]

Portal vein thrombosis is a frequent complication in patients with liver cirrhosis, with a prevalence of about 8% to 25%.[7-9] Portal vein thrombosis results from several local and systemic factors, including decreased portal venous flow, hypercoagulable status, and genetic thrombophilic factors, such as factor V Leiden and prothrombin mutations.[15-17] Cirrhotic patients after splenectomy show decreased levels of ATIII activity, which are associated with hypercoagulable status, and reduced portal venous flow, resulting from the elimination of increased splenic blood flow. This has been found to amplify the incidence of PVT considerably, as much as 24% to 36%.[18,19] Although antithrombotic prophylaxis is recommended for patients at high risk for thrombotic complications, including splenectomy in patients with liver cirrhosis, safe and effective prophylactic methods that do not increase the risk of bleeding have not been identified in cirrhotic patients.

The results of our previous study suggested that prophylactic administration of ATIII concentrates, correcting one of the risk factors for PVT, can prevent PVT without increasing the risks of postoperative hemorrhage after splenectomy.[18] Antithrombin III concentrates can restore the hemostatic balance from a hypercoagulable status to equilibrium. However, it remains unclear whether administration of ATIII concentrates is necessary in all splenectomized patients, or whether ATIII concentrates alone can prevent PVT in patients at higher risk for this complication. We sought to stratify risk levels of PVT after splenectomy in patients with liver cirrhosis and portal hypertension and to establish a prophylactic protocol for preventing PVT. In the testing cohort, we initially determined the cutoff level of preoperative ATIII activity as an indicator of PVT, as described in our previous study,[18] and administered ATIII concentrates based on this cutoff. We re-evaluated the results of the testing cohort by ATIII activity and splenic vein diameter (SVD), which is related to decreased portal venous flow,[19] to stratify the risk levels of PVT, and we developed a prophylactic protocol centered on ATIII concentrates to prevent PVT after splenectomy. In the validation cohort, we validated the stratified risk level of PVT and the prophylactic protocol for PVT after splenectomy in patients with liver cirrhosis and portal hypertension.

METHODS

Testing cohort

Our previous study showed that 9 (36.0%) of 25 cirrhotic patients who received no prophylactic anticoagulation therapy had postoperative PVT develop, and that preoperative low ATIII activity was the most important predictive factor for PVT after splenectomy.[18] Using receiver operating characteristic (ROC) curve analysis to define the cutoff of preoperative ATIII activity to diagnose postoperative PVT in these 25 patients, we found that the area under the ROC curve was 0.852 (Fig. 1). A threshold of ATIII activity $\leq$61% to predict PVT had a sensitivity of 100% and a specificity of 67%; a threshold of ATIII activity $\leq$53% had a sensitivity of 78% and a specificity of 73%; and a threshold of ATIII activity $\leq$48% had a sensitivity of 78% and a specificity of 80%. To reduce the incidence of false negatives as much as possible, the initial criteria for administering ATIII concentrates to prevent PVT was set at ATIII $\leq$60%.

Fifty-three patients (26 male and 27 female; mean age 60.6 $\pm$ 8.6 years; range 39 to 77 years) with liver cirrhosis and portal hypertension who underwent laparoscopic splenectomy in the Department of Surgery, Fukuoka City Hospital from April 2008 to March 2011 were prospectively enrolled (Table 1). Of these patients, 2 had hepatitis B virus–related cirrhosis, 45 had HCV-related cirrhosis, 1