World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/1007-9327office
wjg@wjgnet.com
doi:10.3748/wjg.v18.i26.3443

World J Gastroenterol 2012 July 14; 18(26): 3443-3450
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

BRIEF ARTICLE

Anticoagulation therapy prevents portal-splenic vein thrombosis after splenectomy with gastroesophageal devascularization

Wei Lai, Shi-Chun Lu, Guan-Yin Li, Chuan-Yun Li, Ju-Shan Wu, Qing-Liang Guo, Meng-Long Wang, Ning Li

Wei Lai, Shi-Chun Lu, Guan-Yin Li, Chuan-Yun Li, Ju-Shan Wu, Qing-Liang Guo, Meng-Long Wang, Ning Li, Department of Hepatobiliary Surgery and You-An Liver Transplantation Center, Beijing You-An Hospital, Capital Medical University, Beijing 100069, China

Author contributions: Lai W, Lu SC and Li GY contributed to acquisition, analysis and interpretation of data, drafted the article and revised it critically for important intellectual content; Li CY, Wu JS, Guo QL, Wang ML and Li N contributed to acquisition of data and drafted the article; all authors have read and approved the final version to be published.

Supported by Grants from Beijing Municipal Health Bureau, No. 2011-2-18

Correspondence to: Shi-Chun Lu, Professor, Department of Hepatobiliary Surgery and You-An Liver Transplantation Center, Beijing You-An Hospital, Capital Medical University, Beijing 100069, China. lsc620213@yahoo.com.cn
Telephone: +86-10-63296493 Fax: +86-10-63296493

Received: September 6, 2011 Revised: November 24, 2011
Accepted: March 10, 2012
Published online: July 14, 2012

Abstract

AIM: To compare the incidence of early portal or splenic vein thrombosis (PSVT) in patients treated with irregular and regular anticoagulantion after splenectomy with gastroesophageal devascularization.

METHODS: We retrospectively analyzed 301 patients who underwent splenectomy with gastroesophageal devascularization for portal hypertension due to cirrhosis between April 2004 and July 2010. Patients were categorized into group A with irregular anticoagulation and group B with regular anticoagulation, respectively. Group A (153 patients) received anticoagulant monotherapy for an undesignated time period or with aspirin or warfarin without low-molecular-weight heparin (LMWH) irregularly. Group B (148 patients) received subcutaneous injection of LMWH routinely within the first 5 d after surgery, followed by oral warfarin and aspirin for one month regularly. The target prothrombin time/international normalized ratio (PT/INR) was 1.25-1.50. Platelet and PT/INR were monitored. Color Doppler imaging was performed to monitor PSVT as well as the effectiveness of thrombolytic therapy.

RESULTS: The patients' data were collected and analyzed retrospectively. Among the patients, 94 developed early postoperative mural PSVT, including 63 patients in group A (63/153, 41.17%) and 31 patients in group B (31/148, 20.94%). There were 50 (32.67%) patients in group A and 27 (18.24%) in group B with mural PSVT in the main trunk of portal vein. After the administration of thrombolytic, anticoagulant and antiaggregation therapy, complete or partial thrombus dissolution achieved in 50 (79.37%) in group A and 26 (83.87%) in group B.

CONCLUSION: Regular anticoagulation therapy can reduce the incidence of PSVT in patients who undergo splenectomy with gastroesophageal devascularization, and regular anticoagulant therapy is safer and more effective than irregular anticoagulant therapy. Early and timely thrombolytic therapy is imperative and feasible for the prevention of PSVT.

Key words: Portal vein hypertension; Splenectomy with gastroesophageal devascularization; Portal or splenic vein thrombosis; Anticoagulation regimen; Thrombolytic therapy

Peer reviewer: Kazuhiro Hanazaki, MD, Professor and Chairman, Department of Surgery, Kochi Medical School, Kochi University, Kohasu, Okohcho, Nankoku, Kochi 783-8505, Japan

Lai W, Lu SC, Li GY, Li CY, Wu JS, Guo QL, Wang ML, Li N. Anticoagulation therapy prevents portal-splenic vein thrombo-

sis after splenectomy with gastroesophageal devascularization. *World J Gastroenterol* 2012; 18(26): 3443-3450 Available from: URL: http://www.wjgnet.com/1007-9327/full/v18/i26/3443.htm DOI: http://dx.doi.org/10.3748/wjg.v18.i26.3443

INTRODUCTION

Although endoscopic surgery has been widely used to treat esophagogastric variceal bleeding (EGVB), splenectomy with gastroesophageal devascularization is still the primary method to treat and prevent recurrent EGVB in East Asia[1,2]. Portal or splenic vein thrombosis (PSVT) is a common and potentially life-threatening complication of splenectomy with gastroesophageal devascularization for portal hypertension due to cirrhosis. Severe PSVT can reduce hepatopetal blood flow in the portal system and elevate the blood pressure in the visceral side of portal vein, leading to further deterioration of liver function and the recurrence of upper gastrointestinal (GI) bleeding[3,4]. In serious cases, PSVT can significantly affect patient's life expectancy.

A prospective study with contrast-enhanced computed tomography scan showed that PSVT occurred in 12 (55%) patients of the laparoscopic splenectomy (LS) group, but in only 4 (19%) of the open splenectomy (OS) group, and the difference was significant[5]. A recent clinical study performed by the same group of authors has emphasized that the incidence of PSVT still reached 51.52% in 33 cases after LS without any anticoagulation therapy[6]. The different incidences of PSVT between laparoscopic and open splenectomy may be caused by the operative technique of pneumoperitoneum and ligation of splenic hilar vessels. In the OS group, splenic hilar vessels were ligated conventionally, while these vessels were divided with an endoscopic vascular stapler in the LS group[5]. But in some other studies, the incidence of PSVT varied after splenectomy with gastroesophageal devascularization[7-9].

The literatures mentioned above focused on splenectomy to treat hematologic and metabolic disorders. The reported incidence of PVST related to these diseases may be different from that related to liver cirrhosis because of the different disease spectrum. Kawanaka *et al*[10] analyzed 50 consecutive cirrhotic patients who underwent splenectomy, the PVST incidence was 36.0% (9/25) up to postoperative day (POD) 7 without any prophylactic anticoagulation therapy, the PVST incidence of the other 25 patients was only 4.0% (1/25) up to POD 30 who received antithrombin Ⅲ (AT-Ⅲ) therapy in the first three POD. Ushitora *et al*[11] retrospectively examined 38 consecutive cirrhotic patients who underwent splenectomy, the total incidence of PSVT detected by postoperative dynamic computed tomography was 34.2% (13/38) without any prophylactic anticoagulation therapy. Deng *et al*[12] reported a 33.69% incidence of PVT 7 to 14 d after portal hypertension surgery (splenectomy with gastroesophageal devascularization) in 52 surgically treated patients with portal hypertension due to hepatitis B virus (HBV)-related cirrhosis. The 10-year survival rate among adults with PSVT was 38%-60%, the mortality rate from variceal bleeding in patients with PSVT with cirrhosis was 30%-70%, significantly higher than 5% from variceal bleeding in patients with PSVT without cirrhosis[13].

Therefore, PSVT is indeed a common complication of splenectomy with gastroesophageal devascularization with a high incidence and morbidity even though with different disease spectrum. PSVT was considered contraindicated for liver transplantation in the past because of technical difficulties[14] and currently it still remains as a risk factor[15]. It makes the surgical procedure more cumbersome, resulting in a higher morbidity and mortality in the PSVT patients[16,17]. Englesbe *et al*[18] found that mortality of patients with previous portal vein thrombosis (PVT) after liver transplantation was higher than that of patients without PVT (at 30 d 17.7% *vs* 4.4%, $P = 0.07$; at 1 year 33.0% *vs* 25.0%, $P = 0.354$; and at follow-up 36.7% *vs* 28.4%, $P = 0.371$), even these differences were not statistically significant. And patients with cirrhosis complicated with PVT have significantly increased risks of death after liver transplantation (hazard ratio 7.389, 95% CI: 2.392-22.827).

So, it is very important to prevent the occurrence of PSVT after splenectomy with gastroesophageal devascularization for the better long-term clinical outcomes and following possible liver transplantation. Prophylactic anticoagulation therapy is a prime method to prevent PSVT after splenectomy with gastroesophageal devascularization. The most frequently used drugs are low molecular weight heparin (LMWH), vitamin K antagonist such as warfarin[5], and aspirin[19-21]. But the coarse and dosage of these drugs were variable according to different literatures, there was no generally acceptable PSVT prophylactic regimen for all patients after splenectomy with gastroesophageal devascularization[22,23].

We studied retrospectively the efficacy of regular anticoagulant therapy on preventing early postoperative PSVT in the cirrhotic patients who received splenectomy with gastroesophageal devascularization in Beijing You-An Hospital of Capital Medical University from December 2004 to July 2010.

MATERIALS AND METHODS

Inclusion and exclusion criteria

Inclusion criteria: Patients with liver cirrhosis due to any causes; liver function grade: Child-Pugh A-B; splenomegaly and hypersplenism; severe esophageal varicose confirmed by gastroscopy; and previous histories of recurrent upper gastrointestinal bleeding. All patients signed the informed consent and the study was approved by the Ethics Committee of the hospital. These patients' data within one month after splenectomy with gastroesophageal devascularization were collected and analyzed.

Exclusion criteria: Patients who did not fulfill the inclusion criteria and could not tolerate surgical treatment were excluded.

Clinical examinations

After fasting for 8 h, all patients lied in the supine or left lateral position, and color Doppler ultrasound examination was performed with ACUSON Sequola 512 SIEMENS Ultrasound system with a probe frequency of 3.5 MHz. The inner diameter of the portal vein and the splenic vein were measured in the sagittal position. Platelets/international normalized ratio (PLT/INR) was also measured before surgery and at day 1, day 3, day 7 and 1 mo after surgery.

Surgical procedure and portal venous pressure measurement

Selective gastroesophageal devascularization was performed using intraoperative free portal venous pressure (FPVP) as guidance[24]. A 20G antithrombotic catheter (BD Insyte, Becton Dickinson Medical Devices Co, Ltd. Suzhou, China) was inserted into the right gastro-omental vein to test FPVP after laparotomy and splenectomy, respectively. Gastroesophageal devascularization was performed according to the FPVP.

Treatment and grouping

The patients were classified into two groups according to whether regular anticoagulantion was administered. In group A, the patients received irregular anticoagulant aspirin or warfarin monotherapy for an undesignated time period without LMWH due to poor blood clotting after surgery and perioperative abdominal or GI bleeding.

Patients in group B had nearly normal blood clotting before and after surgery; 24 h after surgery, they received subcutaneous injection of LMWH routinely, 0.3 mL per 12 h for 5 d and then maintained by oral therapy with warfarin for one month to keep the target prothrombin time/international normalized ratio (PT/INR) at a level between 1.25 and 1.5. If the postoperative platelet level was increased to 100×10^9/L or above, aspirin 100 mg daily was added for one month. If the postoperative platelet level was increased to 300×10^9/L or above, ticlopidine was added with the dose of 0.25 g daily for one month.

Color Doppler ultrasound examination and PLT/INR measurement were repeated. Once PSVT was confirmed after splenectomy with gastroesophageal devascularization, the patients would receive a thrombolytic therapy. Urokinase was administered *via* the peripheral venous route with a bonus dose of 200 000 units within 30 min, followed by continuous infusion of 20 000-50 000 units/h for 3-5 d *via* a micro-infusion pump. During the thrombolytic treatment, PT/INR and PLT were measured daily. Following the thrombolytic treatment, the patients were administrated with oral warfarin (2.5 mg, 1-2 times daily) and aspirin (100 mg daily). The drug doses were adjusted according to PT/INR and PLT levels. If repeated color Doppler ultrasound examinations showed complete or partial dissolution of target thrombus, the treatment was considered effective and switched to oral warfarin monotherapy (2.5 mg, 1-2 times daily) for one month. If repeated color Doppler ultrasound examinations showed little change or even enlargement of the target thrombus, the thrombolytic therapy was defined as ineffective. The patients would continue to receive oral warfarin and aspirin and followed up regularly.

Statistical analysis

SPSS version 11.5 software (SPSS Inc., Chicago, IL, United States) was used for statistical analyses. Continuous data were presented as mean ± SD and compared with two-tailed nonpaired Student's t test. Categorical data were analyzed with Chi-square or Fisher exact test. Chronologic changes in the laboratory data were analyzed by the analysis of variance for repeated measures. $P < 0.05$ was considered statistically significant.

RESULTS

A total of 301 cirrhotic patients undergoing splenectomy with gastroesophageal devascularization in our department was included in the study, including 202 males and 99 females with an average age of 45.96 years (range, 14-77 years). They were divided into two groups: Group A, 153 patients, including 103 men and 50 women with a mean age of 46.14 ± 10.39 years; and Group B, 148 patients, including 99 men and 49 women with a mean age of 46.47 ± 9.58 years. There were 254 cases of HBV related cirrhosis, 19 cases of hepatitis C virus related cirrhosis, 22 cases of alcoholic cirrhosis, 3 cases of idiopathic portal hypertension and 3 cases of primary biliary cirrhosis.

As for liver function grade, Child-Pugh A was found in 246 patients and Child-Pugh B in 55 patients. Of the 301 patients, 236 patients (78.40%) had a history of upper GI bleeding before surgery. All major clinical parameters were not significantly different between the two groups (Table 1).

The FPVP before splenectomy was 37.79 ± 5.03 cm H_2O in group A and 36.66 ± 5.24 cm H_2O in group B ($P = 0.179$). The FPVP after splenectomy with gastroesophageal devascularization was 30.01 ± 4.58 cm H_2O in group A and 29.59 ± 4.37 cm H_2O in group B ($P = 0.559$).

Sixteen patients (5.31%) had preoperative spontaneous mural PSVT, with an incidence of 3.92 % (6/153) in group A and 6.76 % (10/148) in group B ($\chi^2 = 1.201$, $P = 0.273$).

The total incidence of postoperative mural PSVT was 31.22 % (94/301), 41.17% (63/153) in group A and 20.94 % (31/148) in group B ($\chi^2 = 15.009$, $P = 0.002$). There were 50 (32.67%) cases of mural thrombi in the main trunk of the portal vein in group A and 27 (18.24%) cases in group B ($P = 0.004$). As shown in Table 2, there was no difference in terms of the location of thrombi between the two groups. No single case of thrombosis involved whole portal system. The incidence of throm-

Table 1 Comparison of preoperative data between two groups

	Irregular anticoagulation (group A)	Regular anticoagulation (group B)	*P* value
Sex (M/F)	103/50	99/49	0.937
Age (yr), mean ± SD	46.14 ± 10.39	46.47 ± 9.58	0.814
Type of disease			
Hepatitis B viral cirrhosis	128	126	0.816
Hepatitis C viral cirrhosis	11	8	
Alcoholic cirrhosis	11	11	
Idiopathic portal hypertension	1	2	
Biliary cirrhosis	2	1	
Child-Pugh classification (grade A/grade B)	121/32	125/23	0.228
MELD index: mean ± SD, median	7.68 ± 3.24, 7.70	6.62 ± 2.76, 6.51	0.055
History of upper GI bleeding	125 (81.69%)	111 (75%)	0.158
History of GI ulcer	18 (11.76%)	23 (15.54%)	0.340
Preoperative portal vein diameter (mm): mean ± SD, median	12.38 ± 1.17, 13	12.90 ± 1.20, 12	0.083
Preoperative splenic vein diameter (mm): mean ± SD, median	9.85 ± 1.69, 10	10.10 ± 1.41, 10	0.551

MELD: Model for end-stage disease; GI: Gastrointestinal.

Table 2 Distribution of thrombi in two groups, *n* (%)

Location	Irregular anticoagulation (group A)	Regular anticoagulation (group B)
Simple PV main trunk mural thrombosis	31 (20.26)	18 (12.16)
Simple splenic vein mural thrombosis	12 (7.84)	4 (2.70)
Complicated portal and splenic vein thrombosis	19 (12.41)	7 (4.72)
Simple SMV thrombosis	1 (0.65)	0
Complicated portal PV and SMV thrombosis	0	2 (1.35)
Total	63	31
Incidence of thrombosis	(41.17)	(20.94)

χ^2 = 15.009, P = 0.002. PV: Portal vein; SMV: Superior mesenteric vein.

bosis in the portal vein main trunk was significantly different between the two groups (χ^2 = 8.236, P = 0.004).

During the anticoagulant therapy, mild GI bleeding occurred in 3 patients, including 1 in group A and 2 in group B. The anticoagulant therapy was terminated immediately and hemostatic agents were administered. Bleeding was successfully controlled, and the patients recovered well.

All 94 patients with postoperative PSVT were treated with thrombolytic drug, urokinase, anticoagulant and antiaggregation agents. Among the 94 patients, 76 achieved complete or partial thrombus dissolution, including 50 (79.37%, 50/63) patients in group A and 26 (83.87%, 26/31) patients in group B (χ^2 = 0.272, P = 0.602). No thrombolytic therapy-related complications such as bleeding were noted.

As shown in Figure 1, platelet count was not significantly different between the two groups (P = 0.981). However, the PT/INR in group B was gradually increased from day 7 after surgery, which was statistically different from that in group A (P = 0.020). We also compared the patients with and without PSVT and found that the PT/INR in patients without PSVT was greater than those with PSVT at day 14 after surgery (1.30 ± 0.21 *vs* 1.23 ± 0.17, P = 0.037). Similar results were found in patients with and without PSVT in group B (1.28 ± 0.21 without PSVT *vs* 1.18 ± 0.14 with PSVT, P = 0.017) (Figure 2).

DISCUSSION

Selection of thrombosis prevention regimens after splenectomy with gastroesophageal devascularization

Currently, a number of studies have suggested possible mechanisms of PSVT formation following splenectomy with gastroesophageal devascularization, including elevated postoperative platelet count, hemodynamic changes in splenic and portal veins, endothelial damage, spleen size, postoperative release of procoagulant factors, the reduction of anticoagulant factors, and the postoperative use of hemostatic drugs[10,25,26]. PSVT may lead to severe clinical adverse events or poor outcomes[3,4]. Therefore, the importance of PSVT prevention has been gradually recognized and emphasized[19-21,27].

Various prevention protocols have been proposed[25,28,29], but the effectiveness of these protocols varied[4,22,30] because the duration and doses of these drugs were variable. Therefore, there was no generally acceptable PSVT prophylactic regimen for all patients[22,23]. There are many blood coagulation factors involved in the formation of thrombosis[31]. Xa is a major factor in the procedure of thrombosis[32,33]. LMWH can suppress factor Xa by combining with ATⅢ to depress the activation of thrombin and formation of thrombosis[34]. LMWH is safer than heparin because of its lower molecular weight, weaker inhibition of factor Ⅱa and longer impact on co-

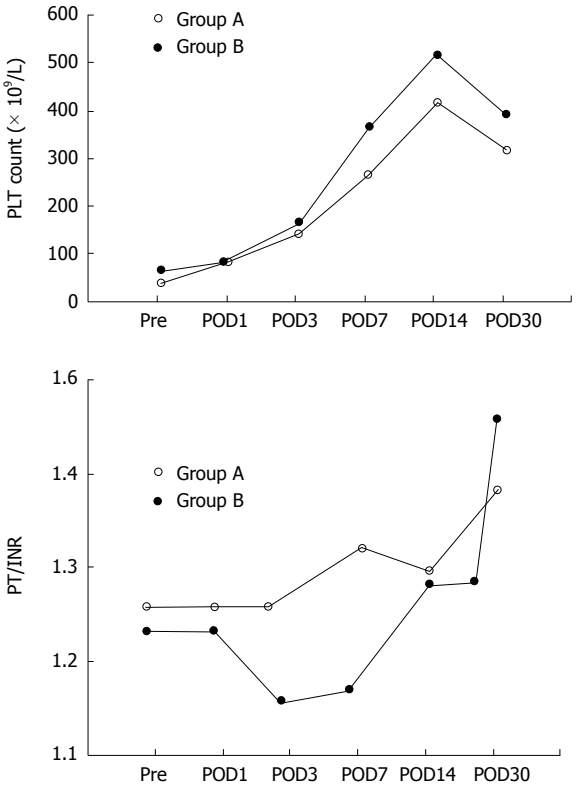

Figure 1 Changes in platelet count and prothrombin time/international normalized ratio in group A and group B. It was not different in platelet (PLT) between the two groups (P = 0.981), but it was statistically different in prothrombin time/international normalized ratio (PT/INR) between the two groups (P = 0.020). PT/INR in group A had no sequential changes pre- and post-operatively (P = 0.479) and PT/INR in group B was increasing gradually from postoperative day 7 with statistical difference (P = 0.003). POD: Postoperative day.

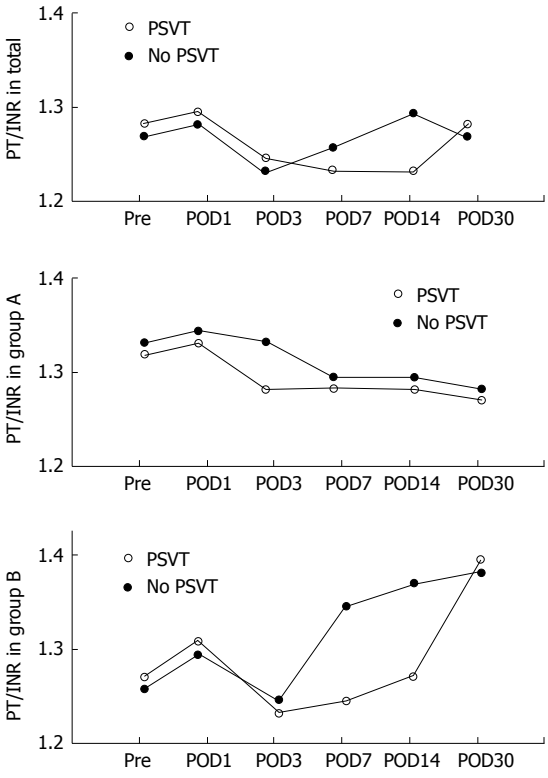

Figure 2 Changes in prothrombin time/international normalized ratio in patients without portal or splenic vein thrombosis and portal or splenic vein thrombosis. In group A, patients with or without portal or splenic vein thrombosis (PSVT) had similar prothrombin time/international normalized ratio (PT/INR), and the difference was not significant between the two subgroups. Patients with or without PSVT presented different PT/INR only at day 14 after surgery, with statistical significance (1.23 ± 0.17 *vs* 1.30 ± 0.21, P = 0.037) by Student's t test. In group B, patients with or without PSVT had different PT/INR only at day 14 after surgery, with statistical significance (1.18 ± 0.14 *vs* 1.28 ± 0.21, P = 0.017) by Student's t test. POD: Postoperative day.

agulation system[35,36].

The increased count and augmented aggregation competence of PLT after operation were important factors related to PSVT[25]. These factors should be taken into account when selecting anticoagulation drugs. Aspirin has been applied in prevention and treatment of thrombotic diseases with satisfied safety because of its anti-PLT aggregation competence[37,38]. Also, warfarin is an important antagonist of vitamin K (VK) with powerful anticoagulation effects by inhibiting VK-depending coagulation factors such as Ⅱ, Ⅶ, Ⅸ, Ⅹ[39,40]. We selected LMWH, warfarin and aspirin as a regular PSVT prevention regimen, which targets the major factors of mechanisms of PSVT. It was reported that the median interval between splenectomy and PSVT was 1-2 wk after surgery[5,22,23,41].

Therefore, we used LMWH for 2-5 d followed by oral warfarin and asprin after surgery in group B. Oral warfarin or aspirin was merely applied to those postoperative patients who were not suitable for LMWH in early postoperative phase as an irregular PSVT prevention regimen in group A.

In this study, we collected and analyzed retrospectively the data about the thrombosis prevention regimens for cirrhotic patients after splenectomy with gastroesophageal devascularization who were treated at our department over the past six years. Our results showed that the early use of LMWH followed by a long-term maintenance therapy with warfarin and aspirin could reduce the incidence of PSVT in group B (20.94%) without causing major bleeding complications, as compared with group A (41.17%) and other studies (51.5%-55%)[5,6]. We also compared the patients with and without PSVT and found that the PT/INR in patients without PSVT was greater than those with PSVT at day 14 after surgery. Similar results were found in patients with and without PSVT in group B, suggesting that our anticoagulant regimen with the PT/INR target value set at 1.25-1.5 was reasonable and effective.

Classification and treatment of PSVT

PSVT in patients with portal hypertension due to cirrhosis following splenectomy with gastroesophageal devascularization can have various clinical manifestations, from no symptoms in mild cases to life-threatening recurrence of upper GI bleeding or small bowel necrosis in serious cases[29]. The difference in clinical consequences stems from the location of PSVT, degree of obstruction, and its impact on portal vein (PV) hemodynamics. In fact, grade Ⅳ PSVT (Yerdel's classification[42]), which involved

PV and superior mesenteric vein (SMV), would result in significant reduction in venous blood return to the liver and elevation in PVP, leading to esophageal and gastric variceal rupture and bleeding. SMV thrombosis can impede venous blood return from the bowels and cause small bowel necrosis, which could be vital for patients.

In this study, all 94 PSVT cases were grade I , which led to almost no clinical manifestations, such as variceal bleeding recurrence and bowel necrosis, and were easy to treat. Thrombolytic therapy has been proven to be effective for acute PSVT. Previous studies have recommended early and timely thrombolytic anticoagulant therapy[43,44] and commonly used drugs, including urokinase, recombinant tissue plasminogen activator (rt-PA), LMWH, warfarin and dipyridamole. Intervention can be categorized by the administration route, i.e., systemic, portal system, and intravascular interventional treatment[45,46]. Krauth *et al*[23] reported that immediate thrombolytic anticoagulant therapy in PSVT patients can achieve a complete dissolution rate of 63.3% and a partial dissolution rate of 13.3%. In our study, thrombolytic therapy *via* the peripheral venous route was administered in all 94 patients with PSVT, among whom 18 patients showed no sign of thrombus dissolution, but 61 patients (64.89%) achieved complete dissolution and 15 patients (15.95%) had partial dissolution. The overall thrombolytic effectiveness in our study was similar to other studies mentioned above. These phenomena were related to the benefit of regular anticoagulant therapy, which confirmed the clinical value of the anticoagulant regimen.

Our findings suggested that regular anticoagulation and early thrombolytic therapy are safe, effective and rational for PSVT patients who had portal hypertension and underwent splenectomy with gastroesophageal devascularization. At present, splenectomy with gastroesophageal devascularization may only be used as a bridge to liver transplantation in cirrhotic patients, timely prevention and thrombolytic treatment for PSVT offers a significant clinical value in terms of facilitating the portal venous reconstruction of the recipients for liver transplantation[47].

Dilemma between anticoagulation and bleeding

Theoretically, preventive use of anticoagulants against PSVT in cirrhotic portal hypertensive patients early after surgery would counter the dilemma of bleeding. But in fact, previous studies have demonstrated that early anticoagulant treatment in these patients is a safe and effective protocol to prevent PSVT[48,49]. Based on our study, the regular monitoring during anticoagulant treatment is necessary, which can guarantee the safety and maintain the PT/INR level between 1.25 and 1.5. Because most of our subjects had end-stage HBV cirrhosis, our suggestion differs from previous studies on non-HBV cirrhotic patients, mostly with hematologic and metabolic disorders and alcoholic cirrhosis, for which, PT/INR value of 2-3 is recommended[50]. In this study, only three patients presented with mild GI bleeding during the anticoagulant treatment. We immediately terminated it and shifted to symptomatic treatment such as hemostatic agents. Bleeding was successfully controlled, and the patients were discharged uneventfully. Therefore, our anticoagulant therapy has been proven safe.

On the other hand, there is a lack of large-scale controlled and long-term studies on the prevention of PSVT in cirrhosis patients receiving splenectomy with gastroesophageal devascularization for splenomegaly and hypersplenism. Since a randomized prospective controlled study is difficult to perform, we choose to conduct this retrospective controlled study. However, randomized controlled trial is necessary in the future.

Complications of splenectomy with gastroesophageal devascularization

Overwhelming postsplenectomy infection (OPSI) syndrome is associated with a high mortality, even it is a rare condition. Major risk factors include the age of the patients with splenectomy, the time after splenectomy, the reason for splenectomy, and the overall immune status of the patients. Splenectomy performed for hematological disorders, including thalassemia, hereditary spherocytosis, autoimmune hemolysis, immune thrombocytopenic purpura, or lymphoma, appears to carry a higher OPSI risk than splenectomy performed as a result of other diseases. Treatment of OPSI is generally aggressive due to the serious nature of the condition and associated mortality. The major preventive strategy is the vaccination using the 23-valent pneumococcal polysaccharide vaccine, a 7-valent proteinconjugated pneumococcal vaccine, the hemophilus influenzae type B vaccine, and the meningococcal vaccine[51]. Fortunately, there was no OPSI occurrence in our study. The reasons may be that all the patients are adults and no splenectomy was performed for hematological disorders, the antibiotic agents were administered for 3-5 d after surgery, and the follow-up period was too short for OPSI.

In summary, the early and regular initiation of anticoagulant treatment using LMWH followed by warfarin and aspirin has been proven safe and effective in early prevention of PSVT in patients with cirrhotic portal hypertension, undergoing splenectomy with gastroesophageal devascularization. The treatment can reduce the incidence of PSVT in the early stage after splenectomy with gastroesophageal devascularization, early and timely thrombolytic therapy is imperative and feasible for the prevention and treatment of PSVT. The protocol presented in our study may benefit the patients not only for approximate and long-term clinical outcome, but also for potential liver transplant candidates in the future. But a better designed randomized prospective study with a longer follow-up period is still needed to clarify our conclusions.

COMMENTS

Background

Portal or splenic vein thrombosis (PSVT) is a common and potentially life-threatening complication of splenectomy with gastroesophageal devascularization for portal hypertension due to cirrhosis, which may lead to further deteriora-

tion of liver function and the recurrence of upper gastrointestinal (GI) bleeding and significantly affects patient's life expectancy. In some severe cases, PSVT may be contraindicated for liver transplantation. It is therefore very important to prevent the occurrence of PSVT after splenectomy with gastroesophageal devascularization to achieve better long-term outcomes and following possible liver transplantation if required.

Research frontiers

Prophylactic anticoagulation therapy using a combination protocol of low molecular weight heparin (LMWH), vitamin K antagonists, such as warfarin and aspirin, is a prime method to prevent PSVT. But the duration and doses of these drugs were variable according to the literature, there was no generally acceptable PSVT prophylactic regimen for all patients after splenectomy with gastroesophageal devascularization. So, a safe and effective prophylactic anticoagulation protocol is needed.

Innovations and breakthroughs

In order to reduce the incidence of PSVT after splenectomy with gastroesophageal devascularization, a regular prophylactic anticoagulation protocol was established with a confirmed monitoring index. This study used the combined and sequential application of LMWH, warfarin, aspirin and ticlopidine according to the regular coagulating function test and color Doppler flow imaging. The incidence and severity of PSVT caused by anticoagulation therapy were reduced, without causing major bleeding complications.

Applications

The study results suggest that prophylactic anticoagulation therapy using LMWH, warfarin and aspirin regularly is a safer and more effective method for PSVT prevention.

Terminology

PSVT is a sort of clinical disease caused by thrombus development in the portal vein system. The major causes of PSVT included the reduced blood flow, the increased platelet count, the injured vessel endothelium and enhanced coagulation function. PSVT is a common complication of abdominal surgery, especially after splenectomy with gastroesophageal devascularization with a high incidence and morbidity.

Peer review

This is a good descriptive study in which authors analyze the preventive effect of prophylactic anticoagulation therapy using low molecular weight heparin, warfarin and aspirin for PSVT. The results are interesting and imply that a regular prophylactic anticoagulation protocol is a safer and more effective method that could be used in preventing PSVT after splenectomy with gastroesophageal devascularization.

REFERENCES

1 **Kinjo N**, Kawanaka H, Akahoshi T, Tomikawa M, Yamashita N, Konishi K, Tanoue K, Shirabe K, Hashizume M, Maehara Y. Risk factors for portal venous thrombosis after splenectomy in patients with cirrhosis and portal hypertension. *Br J Surg* 2010; **97**: 910-916

2 **Yoshida M**, Watanabe Y, Horiuchi A, Yamamoto Y, Sugishita H, Kawachi K. Portal and splenic venous thrombosis after splenectomy in patients with hypersplenism. *Hepatogastroenterology* 2009; **56**: 538-541

3 **Fujita F**, Lyass S, Otsuka K, Giordano L, Rosenbaum DL, Khalili TM, Phillips EH. Portal vein thrombosis following splenectomy: identification of risk factors. *Am Surg* 2003; **69**: 951-956

4 **Amitrano L**, Guardascione MA, Brancaccio V, Margaglione M, Manguso F, Iannaccone L, Grandone E, Balzano A. Risk factors and clinical presentation of portal vein thrombosis in patients with liver cirrhosis. *J Hepatol* 2004; **40**: 736-741

5 **Chaffanjon PC**, Brichon PY, Ranchoup Y, Gressin R, Sotto JJ. Portal vein thrombosis following splenectomy for hematologic disease: prospective study with Doppler color flow imaging. *World J Surg* 1998; **22**: 1082-1086

6 **Skarsgard E**, Doski J, Jaksic T, Wesson D, Shandling B, Ein S, Babyn P, Heiss K, Hu X. Thrombosis of the portal venous system after splenectomy for pediatric hematologic disease. *J Pediatr Surg* 1993; **28**: 1109-1112

7 **Hassn AM**, Al-Fallouji MA, Ouf TI, Saad R. Portal vein thrombosis following splenectomy *Br J Surg* 2000; **87**: 362-373

8 **Ikeda M**, Sekimoto M, Takiguchi S, Kubota M, Ikenaga M, Yamamoto H, Fujiwara Y, Ohue M, Yasuda T, Imamura H, Tatsuta M, Yano M, Furukawa H, Monden M. High incidence of thrombosis of the portal venous system after laparoscopic splenectomy: a prospective study with contrast-enhanced CT scan. *Ann Surg* 2005; **241**: 208-216

9 **Ikeda M**, Sekimoto M, Takiguchi S, Yasui M, Danno K, Fujie Y, Kitani K, Seki Y, Hata T, Shingai T, Takemasa I, Ikenaga M, Yamamoto H, Ohue M, Monden M. Total splenic vein thrombosis after laparoscopic splenectomy: a possible candidate for treatment. *Am J Surg* 2007; **193**: 21-25

10 **Kawanaka H**, Akahoshi T, Kinjo N, Konishi K, Yoshida D, Anegawa G, Yamaguchi S, Uehara H, Hashimoto N, Tsutsumi N, Tomikawa M, Maehara Y. Impact of antithrombin III concentrates on portal vein thrombosis after splenectomy in patients with liver cirrhosis and hypersplenism. *Ann Surg* 2010; **251**: 76-83

11 **Ushitora Y**, Tashiro H, Takahashi S, Amano H, Oshita A, Kobayashi T, Chayama K, Ohdan H. Splenectomy in chronic hepatic disorders: portal vein thrombosis and improvement of liver function. *Dig Surg* 2011; **28**: 9-14

12 **Deng MH**, Liu B, Fang HP, Pan WD, Tang ZF, Deng P, Zhong YS, Xu RY. Predictive value of D-dimer for portal vein thrombosis after portal hypertension surgery in hepatitis B virus-related cirrhosis. *World J Gastroenterol* 2007; **13**: 6588-6592

13 **Wang JT**, Zhao HY, Liu YL. Portal vein thrombosis. *Hepatobiliary Pancreat Dis Int* 2005; **4**: 515-518

14 **Ramos AP**, Reigada CP, Ataíde EC, Almeida JR, Cardoso AR, Caruy CA, Stucchi RS, Boin IF. Portal vein thrombosis and liver transplantation: long term. *Transplant Proc* 2010; **42**: 498-501

15 **Orlando G**, De Luca L, Toti L, Zazza S, Angelico M, Casciani CU, Tisone G. Liver transplantation in the presence of portal vein thrombosis: report from a single center. *Transplant Proc* 2004; **36**: 199-202

16 **Sharma R**, Kashyap R, Jain A, Safadjou S, Graham M, Dwivedi AK, Orloff M. Surgical complications following liver transplantation in patients with portal vein thrombosis--a single-center perspective. *J Gastrointest Surg* 2010; **14**: 520-527

17 **Suarez Artacho G**, Barrera Pulido L, Alamo Martinez JM, Serrano Diez-Canedo J, Bernal Bellido C, Marín Gomez LM, Padillo Ruiz J, Gómez Bravo MA. Outcomes of liver transplantation in candidates with portal vein thrombosis. *Transplant Proc* 2010; **42**: 3156-3158

18 **Englesbe MJ**, Kubus J, Muhammad W, Sonnenday CJ, Welling T, Punch JD, Lynch RJ, Marrero JA, Pelletier SJ. Portal vein thrombosis and survival in patients with cirrhosis. *Liver Transpl* 2010; **16**: 83-90

19 **Wang H**, Kopac D, Brisebois R, Sample C, Shapiro AM. Randomized controlled trial to investigate the impact of anticoagulation on the incidence of splenic or portal vein thrombosis after laparoscopic splenectomy. *Can J Surg* 2011; **54**: 227-231

20 **Stamou KM**, Toutouzas KG, Kekis PB, Nakos S, Gafou A, Manouras A, Krespis E, Katsaragakis S, Bramis J. Prospective study of the incidence and risk factors of postsplenectomy thrombosis of the portal, mesenteric, and splenic veins. *Arch Surg* 2006; **141**: 663-669

21 **Amitrano L**, Guardascione MA. Management of portal vein thrombosis in cirrhotic patients. *Mediterr J Hematol Infect Dis* 2009; **1**: e2009014

22 **Ponziani FR**, Zocco MA, Campanale C, Rinninella E, Tortora A, Di Maurizio L, Bombardieri G, De Cristofaro R, De Gaetano AM, Landolfi R, Gasbarrini A. Portal vein thrombosis: insight into physiopathology, diagnosis, and treatment. *World J Gastroenterol* 2010; **16**: 143-155

23 **Krauth MT**, Lechner K, Neugebauer EA, Pabinger I. The postoperative splenic/portal vein thrombosis after splenectomy and its prevention--an unresolved issue. *Haematologica* 2008; **93**: 1227-1232

24 **Sun YW**, Chen W, Luo M, Hua R, Liu W, Huo YM, Wu ZY, Cao H. Evaluation of surgical procedure selection based on intraoperative free portal pressure measurement in patients with portal hypertension. *Hepatobiliary Pancreat Dis Int* 2010; **9**: 269-274

25 **Zocco MA**, Di Stasio E, De Cristofaro R, Novi M, Ainora ME, Ponziani F, Riccardi L, Lancellotti S, Santoliquido A, Flore R, Pompili M, Rapaccini GL, Tondi P, Gasbarrini GB, Landolfi R, Gasbarrini A. Thrombotic risk factors in patients with liver cirrhosis: correlation with MELD scoring system and portal vein thrombosis development. *J Hepatol* 2009; **51**: 682-689

26 **Sogaard KK**, Astrup LB, Vilstrup H, Gronbaek H. Portal vein thrombosis; risk factors, clinical presentation and treatment. *BMC Gastroenterol* 2007; **7**: 34

27 **Spahr L**, Boehlen F, de Moerloose P, Hadengue A. Anticoagulants in portal vein thrombosis: don't be so shy! *Blood* 2009; **113**: 5031-5032; author reply 5032

28 **Romano F**, Caprotti R, Conti M, Piacentini MG, Uggeri F, Motta V, Pogliani EM, Uggeri F. Thrombosis of the splenoportal axis after splenectomy. *Langenbecks Arch Surg* 2006; **391**: 483-488

29 **Rattner DW**, Ellman L, Warshaw AL. Portal vein thrombosis after elective splenectomy. An underappreciated, potentially lethal syndrome. *Arch Surg* 1993; **128**: 565-569; discussion 569-570

30 **Park AE**, Birgisson G, Mastrangelo MJ, Marcaccio MJ, Witzke DB. Laparoscopic splenectomy: outcomes and lessons learned from over 200 cases. *Surgery* 2000; **128**: 660-667

31 **Woodruff RS**, Sullenger B, Becker RC. The many faces of the contact pathway and their role in thrombosis. *J Thromb Thrombolysis* 2011; **32**: 9-20

32 **Romualdi E**, Ageno W. Investigational factor Xa inhibitors for thrombosis and acute coronary syndromes. *Expert Opin Investig Drugs* 2011; **20**: 495-505

33 **Orfeo T**, Butenas S, Brummel-Ziedins KE, Gissel M, Mann KG. Anticoagulation by factor Xa inhibitors. *J Thromb Haemost* 2010; **8**: 1745-1753

34 **Turpie AG**. Pharmacology of the low-molecular-weight heparins. *Am Heart J* 1998; **135**: S329-S335

35 **Hirsh J**, Warkentin TE, Shaughnessy SG, Anand SS, Halperin JL, Raschke R, Granger C, Ohman EM, Dalen JE. Heparin and low-molecular-weight heparin: mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy, and safety. *Chest* 2001; **119**: 64S-94S

36 **Bechmann LP**, Sichau M, Wichert M, Gerken G, Kröger K, Hilgard P. Low-molecular-weight heparin in patients with advanced cirrhosis. *Liver Int* 2011; **31**: 75-82

37 **Paikin JS**, Wright DS, Eikelboom JW. Effectiveness and safety of combined antiplatelet and anticoagulant therapy: a critical review of the evidence from randomized controlled trials. *Blood Rev* 2011; **25**: 123-129

38 **Bollati M**, Gaita F, Anselmino M. Antiplatelet combinations for prevention of atherothrombotic events. *Vasc Health Risk Manag* 2011; **7**: 23-30

39 **Kuzniatsova N**, Lip GY. Combined antiplatelet therapy and oral anticoagulation: is a balance between thromboembolism and bleeding possible? *Int J Cardiol* 2011; **148**: 1-3

40 **Mavrakanas T**, Bounameaux H. The potential role of new oral anticoagulants in the prevention and treatment of thromboembolism. *Pharmacol Ther* 2011; **130**: 46-58

41 **van't Riet M**, Burger JW, van Muiswinkel JM, Kazemier G, Schipperus MR, Bonjer HJ. Diagnosis and treatment of portal vein thrombosis following splenectomy. *Br J Surg* 2000; **87**: 1229-1233

42 **Yerdel MA**, Gunson B, Mirza D, Karayalçin K, Olliff S, Buckels J, Mayer D, McMaster P, Pirenne J. Portal vein thrombosis in adults undergoing liver transplantation: risk factors, screening, management, and outcome. *Transplantation* 2000; **69**: 1873-1881

43 **Winslow ER**, Brunt LM, Drebin JA, Soper NJ, Klingensmith ME. Portal vein thrombosis after splenectomy. *Am J Surg* 2002; **184**: 631-635; discussion 635-636

44 **Ponziani FR**, Zocco MA, Tortora A, Gasbarrini A. Is there a role for anticoagulants in portal vein thrombosis management in cirrhotic patients? *Expert Opin Pharmacother* 2010; **11**: 1479-1487

45 **Schäfer C**, Zundler J, Bode JC. Thrombolytic therapy in patients with portal vein thrombosis: case report and review of the literature. *Eur J Gastroenterol Hepatol* 2000; **12**: 1141-1145

46 **Lopera JE**, Correa G, Brazzini A, Ustunsoz B, Patel S, Janchai A, Castaneda-Zuniga W. Percutaneous transhepatic treatment of symptomatic mesenteric venous thrombosis. *J Vasc Surg* 2002; **36**: 1058-1061

47 **Pan C**, Shi Y, Zhang JJ, Deng YL, Zheng H, Zhu ZJ, Shen ZY. Single-center experience of 253 portal vein thrombosis patients undergoing liver transplantation in China. *Transplant Proc* 2009; **41**: 3761-3765

48 **Condat B**, Pessione F, Helene Denninger M, Hillaire S, Valla D. Recent portal or mesenteric venous thrombosis: increased recognition and frequent recanalization on anticoagulant therapy. *Hepatology* 2000; **32**: 466-470

49 **Soyer T**, Ciftci AO, Tanyel FC, Senocak ME, Büyükpamukçu N. Portal vein thrombosis after splenectomy in pediatric hematologic disease: risk factors, clinical features, and outcome. *J Pediatr Surg* 2006; **41**: 1899-1902

50 **Webster GJ**, Burroughs AK, Riordan SM. Review article: portal vein thrombosis -- new insights into aetiology and management. *Aliment Pharmacol Ther* 2005; **21**: 1-9

51 **Okabayashi T**, Hanazaki K. Overwhelming postsplenectomy infection syndrome in adults - a clinically preventable disease. *World J Gastroenterol* 2008; **14**: 176-179

S- Editor Cheng JX **L- Editor** Ma JY **E- Editor** Li JY