

Follow-up results of acute portal and splenic vein thrombosis with or without anticoagulation therapy after hepatobiliary and pancreatic surgery

Chan Woo Cho, Yang Jin Park, Young-Wook Kim, Sung Ho Choi, Jin Seok Heo, Dong Wook Choi, Dong-Ik Kim

Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Purpose: Acute portal and splenic vein thrombosis (APSVT) after hepatobiliary and pancreatic (HBP) surgery is a rare but serious complication and a treatment strategy has not been well established. To assess the safety and efficacy of anticoagulation therapy for treating APSVT after HBP surgery.

Methods: We performed a retrospective case-control study of 82 patients who were diagnosed with APSVT within 4 weeks after HBP surgery from October 2002 to November 2012 at a single institute. We assigned patients to the anticoagulation group (n = 32) or nonanticoagulation group (n = 50) and compared patient characteristics, complications, and the recanalization rate of APSVT between these two groups.

Results: APSVT was diagnosed a mean of 8.6 ± 4.8 days after HBP surgery. Patients' characteristics were not significantly different between the two groups. There were no bleeding complications related to anticoagulation therapy. The 1-year cumulative recanalization rate of anticoagulation group and nonanticoagulation group were 71.4% and 34.1%, respectively, which is statistically significant (log-rank test, $P = 0.0001$). In Cox regression model for multivariate analysis, independent factors associated with the recanalization rate of APSVT after HBP surgery were anticoagulation therapy ($P = 0.003$; hazard ratio [HR], 2.364; 95% confidence interval [CI], 1.341–4.168), the absence of a vein reconstruction procedure ($P = 0.027$; HR, 2.557; 95% CI, 1.111–5.885), and operation type (liver resection rather than pancreatic resection; $P = 0.005$, HR, 2.350; 95% CI, 1.286–4.296).

Conclusion: Anticoagulation therapy appears to be a safe and effective treatment for patients with APSVT after HBP surgery. Further prospective studies of larger patient populations are necessary to confirm our findings.

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Key Words: Thrombosis, Mesentery, Surgery, Portal vein, Anticoagulants

INTRODUCTION

Abdominal intervention such as hepatobiliary and pancreatic (HBP) surgery is known to be a risk factor associated with acute portal and splenic vein thrombosis (APSVT). A recent study reported that abdominal surgeries accounted for up to 20% of all cases of acute portal vein thrombosis (PVT) [1]. APSVT after HBP surgery is a rare but serious complication. The incidence

of acute PVT was reported to be 5% in patients who underwent portal vein reconstruction during pancreaticoduodenectomy [2,3]. Thrombus extension to the mesenteric vein can cause bowel infarction, with a reported mortality of 20% to 50% [4].

Despite its potentially poor outcomes, treatment strategy for APSVT after HBP surgery has not been well established, and most surgeons are reluctant to initiate anticoagulation therapy due to concern about the risk of postoperative bleeding.

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Corresponding Author: Yang Jin Park

Division of Vascular Surgery, Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 135-710, Korea

Tel: +82-2-3410-1781, Fax: +82-2-3410-0040

E-mail: yjpark1974@gmail.com

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However, recently, we became to have the patients with more advanced stage and had to perform more radical curative resection for them. And also, since there have been many reports about the safety of anticoagulation therapy after liver transplantation, we have started positively anticoagulation therapy for those patients with APSVT after HBP surgery.

Our aim in this study was to assess the safety and efficacy of anticoagulation therapy to treat APSVT after HBP surgery in terms of bleeding complications and recanalization rate and to identify factors associated with recanalization after anticoagulation.

METHODS

This retrospective study included all patients who had been diagnosed with APSVT within 4 weeks of HBP surgery from October 2002 to November 2012 at Samsung Medical Center in Korea. The study protocol was approved by the Institutional Review Board of Samsung Medical Center and informed consent was waived.

APSVT was diagnosed on the basis of a follow-up CT scan after HBP surgery according to routine clinical pathway. Patients who had portal or splenic vein thrombosis before surgery, preoperative presence of a tumor thrombus, or cavernous trans-

formation were excluded. We also excluded patients who were diagnosed with APSVT more than four weeks after surgery regarding as exceeding acute phase of thrombus immediate after surgery, and those who were lost to follow-up without CT for reassessment of thrombosis, operative mortality cases regardless of anticoagulation therapy because of the uncertain judgment about the efficacy of anticoagulation therapy. Moreover, patients were excluded if they were diagnosed with only a vein stump thrombus at the resection site without other thrombi, because it does not affect the portal blood stream.

Definition

Date of diagnosis corresponded to the date of the follow-up CT study. All CT images for final diagnosis of APSVT were reviewed by two expert radiologists. Obstruction was defined as the presence of solid material in the vascular lumen or its obliteration [5]. If obstruction of portal or splenic vein existed, more than two expert radiologists differentiated between benign and malignant thrombus based on the following CT characteristics: (1) intrathrombus neovascularity; (2) venous expansion (main portal vein diameter greater than or equal to 23 mm); and (3) direct invasion of the portal vein [6].

Following Yerdel et al. [7], we retrospectively graded APSVT as follows: grade 1, <50% PVT +/- minimal obstruction of the

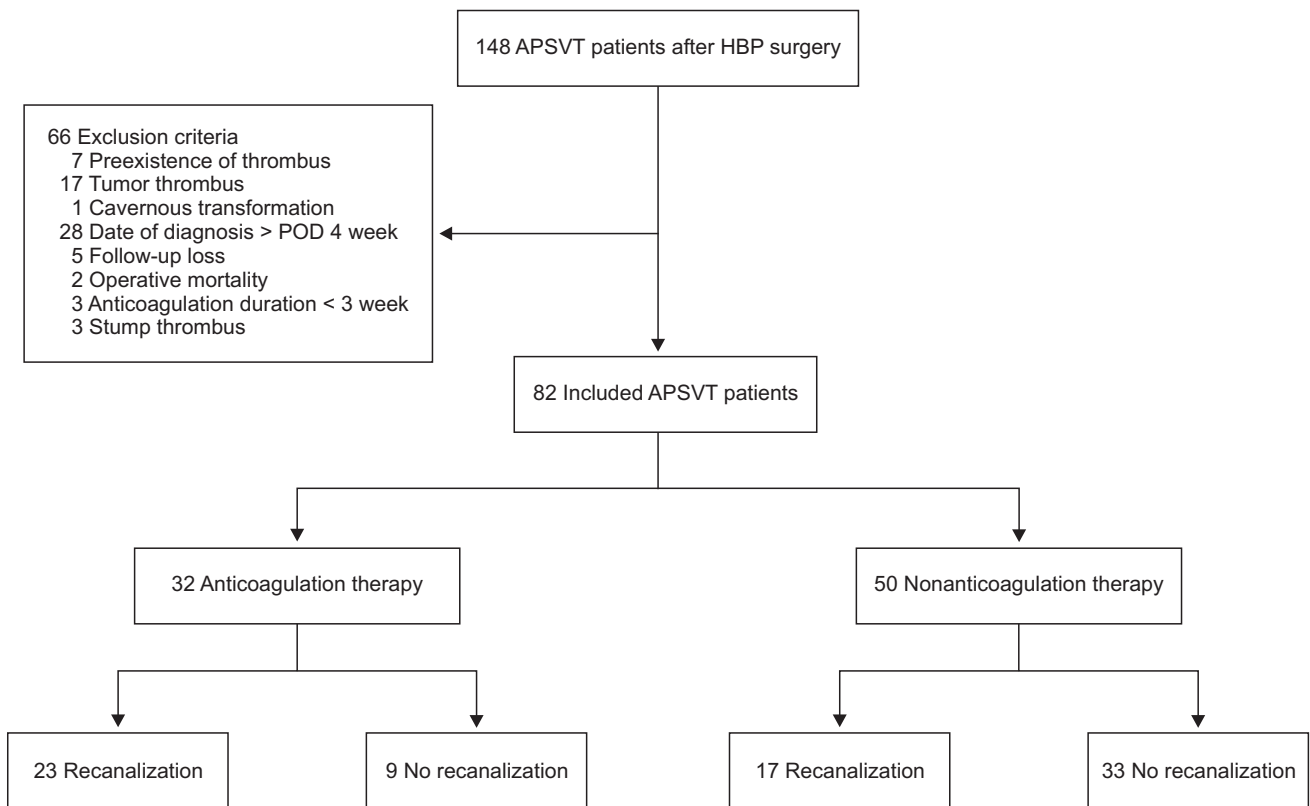


Fig. 1. Study design and outcomes of anticoagulation and no anticoagulation group. APSVT, acute portal and splenic vein thrombosis; HBP, hepatobiliary and pancreatic; POD, postoperative day.

superior mesenteric vein (SMV); grade 2, grade 1 but >50% PVT; grade 3, complete PV and proximal SMV thrombosis; grade 4, complete PV and entire SMV thrombosis. Moreover, isolated splenic vein thrombosis without portal vein thrombosis was graded as grade 0.

Generally speaking, anticoagulation therapy was indicated for the patients with symptom such as abdominal pain, venous reconstruction during operation, and any sign of bowel ischemia on CT scan. Anticoagulation therapy was initiated with low molecular weight heparin (LMWH) and converted to oral vitamin K antagonists (VKA) in 32 patients. The target international normalized ratio (INR) on VKA was set between 2 and 3. If the INR value was reached to the target level, patient stopped subcutaneous injection of LMWH and took only VKA. Oral VKA was prescribed for 3 or 6 months in usual cases. If there was the evidence of early recanalization during the follow-up period, anticoagulation was stopped prior to 3 or 6 months.

Primary endpoint was recanalization of APSVT after

HBP surgery, and recanalization was defined as the normal appearance of a previously occluded segment [5].

Major hepatectomy was defined as resection of four or more liver segments, while minor hepatectomy was defined as resection of less than three liver segments [8]. Pancreatic resection was classified according to the extent and site of resection as total, head, or tail resection.

Statistical methods

Student t-test was used to compare quantitative data, while the chi-square test or Fisher exact test was used to compare qualitative data. Using Cox-regression analysis, we examined the effect of all predictable variables on the recanalization of APSVT after HBP surgery. The variables examined were: age, gender, anticoagulation therapy, liver cirrhosis, operation time, diagnosis interval, postoperative fluid collection, vein reconstruction, operation type, APSVT grade, and original disease. All the factors clinically relevant to the recanalization

Table 1. Patient characteristic

Characteristic	Anticoagulation (n = 32)	Nonanticoagulation (n = 50)	P-value
Age (yr)	58.9 ± 13.0	60.2 ± 10.9	0.610
Male gender	32 (64.0)	18 (60.0)	0.483
Diagnosis interval ^{a)} (day)	8.8 ± 4.6	8.5 ± 4.9	0.825
Follow-up (day)	214.0 ± 347.3	209.5 ± 296.2	0.950
Recanalization	23 (71.4)	17 (34.1)	0.003
Liver cirrhosis	2 (6.2)	7 (14.0)	0.471
Postoperative fluid collection	27 (84.4)	35 (70.0)	0.139
Postoperative bleeding ^{b)}	0 (0)	0 (0)	NA
APSVT grade ^{c)}			0.135
0	0 (0)	6 (12.0)	
1	25 (78.1)	36 (72.9)	
2	6 (18.8)	7 (14.0)	
3	1 (3.1)	1 (2.0)	
Lab values at diagnosis date (n) ^{d)}			
WBC (×10 ³ /μL) (n = 82)	8.073 ± 3.204	7.684 ± 4.450	0.670
Hemoglobin (g/dL) (n = 82)	10.6 ± 1.6	10.4 ± 1.4	0.568
CRP (mg/dL) (n = 69)	3.05 ± 2.26	4.59 ± 3.89	0.042
Albumin (g/dL) (n = 79)	3.16 ± 0.29	3.15 ± 0.37	0.866
Total bilirubin (mg/dL) (n = 81)	0.9 ± 0.6	2.5 ± 4.3	0.009
AST (U/L) (n = 81)	31.8 ± 21.3	44.3 ± 36.2	0.054
ALT (U/L) (n = 81)	36.6 ± 25.9	58.9 ± 54.0	0.015
Amylase (U/L) (n = 59)	64.3 ± 60.1	81.4 ± 87.9	0.418
Lipase (U/L) (n = 59)	39.3 ± 39.2	40.5 ± 60.2	0.933
Symptoms			0.270
Asymptomatic	22 (68.8)	38 (76.0)	
Abdominal pain	8 (25.0)	6 (12.0)	
Fever	1 (3.1)	2 (4.0)	
Nausea	0 (0)	3 (6.0)	
Diarrhea	0 (0)	1 (2.0)	
Abdominal pain and nausea	1 (3.1)	0 (0)	

Values are presented as mean ± standard deviation or number (%).

APSVT, acute portal and splenic vein thrombosis; SMV, superior mesentery; PVT, portal vein thrombosis; NA, not applicable.

^{a)}Defined as duration between operation and diagnosis date. ^{b)}Defined as requiring reoperation for bleeding control. ^{c)}Grade 0, only SVT; grade 1, <50% PVT +/- minimal obstruction of SMV; grade 2, grade 1 but >50% PVT; grade 3, complete PV and proximal SMV thrombosis. ^{d)}No. of patient who performed laboratory test at diagnosis date.

rate, and those that showed even a slight effect on patency ($P < 0.25$) in univariate analysis were included in the model of multivariate analysis. The multivariate analysis used was the proportional hazards model or Cox regression analysis in order to identify independent factors of recanalization. The statistical differences between the recanalization curves of the anticoagulation group and nonanticoagulation group were calculated using the log-rank test. All reported P-value were two-tailed and considered significant if less than 0.05. Data handling and analysis were performed using SPSS ver. 16.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

APSVT was diagnosed on CT scan in 148 of 5,295 patients

(2.8%) who underwent HBP surgery. After exclusion of sixty-six patients, we finally included 82 patients in this study, of whom 32 received anticoagulation treatment and 50 were observed without anticoagulation (Fig. 1).

APSVT was diagnosed in a mean of 8.6 ± 4.8 days after HBP, and the mean initiation date of anticoagulation therapy was postoperative 10.3 ± 6.8 days. There were no statistically significant differences in patient's demographics, diagnosis date of APSVT, and follow-up duration between the anticoagulation and nonanticoagulation groups. However, patients in the non-anticoagulation group had a higher CRP value ($P = 0.042$), total bilirubin level ($P = 0.009$), and ALT level ($P = 0.015$) in laboratory tests at the time of diagnosis (Table 1). There was no bleeding complication associated with or without anticoagulation.

Table 2. Disease-related and operative data

Variable	Anticoagulation (n = 32)	Nonanticoagulation (n = 50)	P-value
Operation type			0.255
HPD	1 (3.1)	3 (6.0)	
Hepatic resection			
Major hepatectomy	3 (9.4)	14 (28.0)	
Minor hepatectomy	6 (18.8)	10 (20.0)	
Wedge resection	2 (6.2)	1 (2.0)	
Pancreatic resection			
Total pancreatectomy	3 (9.4)	1 (2.0)	
Head resection (WP, PPPD)	14 (43.8)	16 (32.0)	
Tail resection (DP, RAMPS)	3 (9.4)	5 (10.0)	
Operation time (min)	320.7 ± 140.3	350.5 ± 148.7	0.368
Vein reconstruction	11 (34.4)	8 (16.0)	0.054
Lateral venorrhaphy	1 (3.1)	1 (2.0)	
Primary end-to-end anastomosis	8 (25.0)	5 (10.0)	
Allograft	2 (6.3)	1 (2.0)	
Autologous vein graft	0	1 (2.0)	
Original disease			0.649
Liver disease			
Benign			
IHD stone	1 (3.1)	0 (0)	
Malignancy			
Hepatocellular carcinoma	3 (9.4)	10 (20.0)	
Cholangiocarcinoma	2 (6.2)	4 (8.0)	
IPNB	0 (0)	1 (2.0)	
Metastatic liver disease	4 (12.2)	8 (16.0)	
Extrahepatic Bile duct disease			
Malignancy			
Bile duct cancer	2 (6.2)	4 (8.0)	
Gallbladder cancer	2 (6.2)	4 (8.0)	
Pancreas disease			
Benign			
Chronic pancreatitis	1 (3.1)	0 (0)	
Malignancy			
Cystic neoplasm	5 (15.6)	2 (4.0)	
PDAC	7 (21.9)	12 (24)	
Other malignancy	2 (6.2)	2 (4.0)	
Other primary malignancy	3 (9.4)	3 (6.0)	

Values are presented as number (%) or mean \pm standard deviation.

HPD, hepatopancreatoduodenectomy; WP, Whipple's operation; PPPD, pylorus preserving pancreaticoduodenectomy; DP, distal pancreatectomy; RAMPS, radical antegrade modular pancreatectomy; IHD, intrahepatic duct; IPNB, Intraductal papillary neoplasm of the bile duct; PDAC, pancreatic ductal adenocarcinoma.

Disease-related and operative data such as operation type, operation time, presence of vein reconstruction procedure and original disease did not show any significant differences between two groups (Table 2).

Mean follow-up time was 211.3 ± 315.0 days, which is not different between two groups (214.0 ± 347.3 in anticoagulation group, 209.5 ± 296.2 in nonanticoagulation group). Fig. 2 shows that a 1-year cumulative recanalization rate of APSVT in anticoagulation group and nonanticoagulation group was 71.4% and 34.1%, respectively, which was statistically significant in multivariate Cox-regression model ($P = 0.003$; hazard ratio [HR], 2.364; 95% confidence interval [CI], 1.341–4.168).

By stepwise exclusion of the variables that had the least significant relationship to the outcome, operation type (liver resection rather than pancreatic resection), anticoagulation therapy,

and the absence of vein reconstruction were independently associated with a higher recanalization rate (Table 3).

DISCUSSION

In our study of 82 patients with APSVT after HBP surgery, we sought to answer two important questions. Is anticoagulation therapy safe for the patients postoperatively, and effective in terms of recanalization?

With regard to the safety of anticoagulation therapy, we observed no major bleeding complications in the 32 patients treated with an anticoagulant agent. Previous studies reported that the incidence of warfarin-induced major bleeding ranged from 0.4% to 7.2% per year [9-11]. Although the incidence of gastrointestinal bleeding in patients diagnosed with portal vein thrombosis has been reported to be 125 per 100 patient-years, anticoagulation therapy did not increase the risk or severity of bleeding [12]. However, numerous patient-specific factors can alter metabolism [13], and the first 90 days are the most variable with regard to the level of anticoagulation as the INR can be labile, which can contribute to bleeding risk [9,14]. Therefore, each patient should be assessed individually prior to starting anticoagulation therapy with emphasis on careful monitoring and patient education about medication [9].

Another major finding in this study was that patients who received anticoagulation therapy had a significantly higher 1-year recanalization rate of APSVT after HBP surgery than patients who did not receive anticoagulation therapy (71.4% vs. 34.1%, $P = 0.003$; HR, 2.364; 95% CI, 1.341–4.168) as shown in Fig. 2. Mean initiation date of anticoagulation was 10.3 ± 6.8 days after HBP surgery. These results are consistent with the results of earlier studies; these studies reported that recanalization occurred in one-third of patients who were

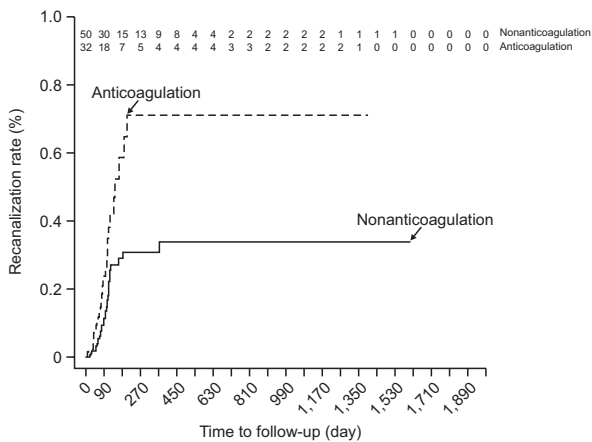


Fig. 2. A significant association between recanalization rate and anticoagulation in multivariate Cox-regression model ($P = 0.003$; hazard ratio, 2.364; 95% confidence interval, 1.341–4.168).

Table 3. Univariate and multivariate analysis of factors predicting recanalization of APSVT

Variable	No. (n = 82)	Univariate			Multivariate		
		HR	95% CI	P-value	HR	95% CI	P-value
Age < 60 yr	34	0.878	0.518–1.489	0.629	-	NA	-
Male gender	50	1.027	0.600–1.758	0.923	-	NA	-
Anticoagulation therapy	32	1.473	0.870–2.492	0.149	2.364	1.340–4.168	0.003
Liver cirrhosis	9	1.091	0.467–2.550	0.840	0.529	0.215–1.304	0.167
Operation time (min) < 340	42	1.649	0.963–2.823	0.068	-	NA	-
Diagnosis interval (day) > 9	49	0.584	0.250–1.363	0.214	0.486	0.196–1.206	0.120
Postoperative fluid collection	62	1.046	0.562–1.946	0.888	-	NA	-
No vein reconstruction	63	2.273	1.071–4.824	0.033	2.557	1.110–5.885	0.027
Hepatic resection only ^{a)}	36	2.508	1.462–4.302	0.001	2.351	1.286–4.295	0.005
APSVT grade 0 + 1	67	1.582	0.773–3.234	0.209	-	NA	-
Original liver disease	33	1.954	0.149–3.326	0.013	-	NA	-

APSVT, acute portal and splenic vein thrombosis; HR, hazard ratio; CI, confidence interval; NA, not applicable.

^{a)}Exclude four hepatopancreatoduodenectomy operations.

given anticoagulation therapy for acute portal vein thrombosis, and that the rate of recanalization was influenced by early anticoagulation therapy [5,15]. Despite of the retrospective nature of our study, this is first study to statistically assess the correlation between anticoagulation therapy and recanalization of APSVT in selected patients who underwent recent HBP surgery. There was no significant relationship between recanalization rate and APSVT grade in the 82 patients we evaluated. This finding is in contrast to the results of Condat et al. [15] who reported that the probability of recanalization was related to the extent of thrombosis. Future work will focus on predicting recanalization of APSVT according to the extent of thrombosis by establishing appropriate classification criteria for APSVT.

No patients in our study cohort had clinical manifestations of potential bowel ischemia at the time of diagnosis of APSVT. Of the 82 patients, 80 had an APSVT grade below 2, indicating the absence of complete or extensive obstructions, which is the reason why there was no mortality in our series, compared to other reports. Complete or extensive obstructions, such as grade 3 or 4 APSVT, may lead to potential bowel ischemia and liver dysfunction. Appropriate alternative therapies, such as site-directed thrombolytic therapy or operative and mechanical thrombectomy, are necessary in these cases [16-22].

Multivariate analysis revealed that along with anticoagulation treatment, the absence of vein reconstruction was significantly associated with recanalization of APSVT ($P = 0.027$; HR, 2.557; 95% CI, 1.111–5.885). Literature documenting portal vein thrombosis rates in patients with venous reconstruction is sparse. Previous reports suggested that acute thrombosis occurs in 5.0% to 6.9% of reconstructions [2,23]. Not performing a vein reconstruction procedure resulted in a significantly higher recanalization rate than performing a vein reconstruction procedure. Performance of venous reconstruction was also closely correlated with a longer operation time and an increased risk of inflammation. It appears that vein resection and reconstruction procedures increase the risk of infection and direct injury to the porto-mesenteric venous system during manipulation [24,25]. In our analysis, 19 patients underwent vein reconstructions, and these patients had a significantly longer operation time than the other patients ($P = 0.001$; HR, 8.667; 95% CI, 2.283–32.895). Although there was no significant correlation between vein reconstruction and laboratory test results, the 19 patients

who underwent vein reconstruction had higher WBC counts and CRP values than the 63 patients who did not undergo vein reconstruction. Poor outcomes of the vein resection group are in accordance with those of several previous studies that reported no significant difference in the rate of portal thrombosis between patients undergoing anticoagulation and patients who did not receive anticoagulation therapy [2,26,27].

In addition, APSVT after liver resection showed higher recanalization rate than that after pancreatic resection. In our opinion, the reason could be that the lesser extensive dissection around portomesenteric trees and the lower inflammation resulted in the higher responsiveness to the anticoagulation therapy.

Although our results are clinically relevant, the limitations of this study must be acknowledged. First, because this was retrospective study, the patient population was heterogeneous, that is, the former patients received less anticoagulation therapy. And the indication of anticoagulation therapy was vague in the medical records in many patients. Second, this study included patients who underwent heterogeneous HBP surgeries from hepatopancreaticoduodenectomy to hepatic tumorectomy. With the exception of two patients, most patients were diagnosed with various malignancies, ranging from hepatocellular carcinoma to pancreas cystadenoma. We were therefore notable to evaluate the relevance of the TNM stage of malignant diseases on recanalization or anticoagulation therapy success. Despite of the heterogeneous nature of the underlying diseases, the cohort that received anticoagulation therapy was smaller than the cohort not treated with anticoagulation therapy ($n = 32$ vs. $n = 50$, respectively). Prospective studies that are disease-specific and that evaluate a larger population of patients are required to confirm the effects of anticoagulation therapy in APSVT.

In conclusion, our results provide the evidence that early anticoagulation therapy to treat APSVT after HBP surgery is not associated with post-operative bleeding and effective in restoring portal vein flow without thrombus propagation.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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