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Original Research

Warfarin versus aspirin prevents portal vein thrombosis after laparoscopic splenectomy and azygoportal disconnection: A randomized clinical trial☆

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ABSTRACT

Introduction: Portal vein system thrombosis (PVST) is a common, potentially life-threatening complication after splenectomy. The optimal recognized anticoagulation drugs for preventing PVST in cirrhotic patients after splenectomy remain unclear. The aim of this study is to evaluate the safety and efficacy of warfarin in preventing PVST after laparoscopic splenectomy and azygoportal disconnection (LSD).

Methods: In this randomized controlled single-center study, 80 cirrhotic patients who underwent LSD were randomly assigned to 2 years of treatment with either warfarin (n = 40) or aspirin (n = 40). The primary outcome was prevention of PVST. Sonographers and radiologists who assessed outcomes were blinded to group assignments. Intention-to-treat analysis was performed.

Results: During the first year, excluding two patients withdrawing from the study, 15 of the 39 warfarin-treated patients (38.5%) and five of the 39 aspirin-treated patients (12.8%) did not develop PVST ($P = 0.010$). The incidence of PVST in the first 2 postoperative years was significantly lower in the warfarin group than in the aspirin group ($F = 7.360$, $P = 0.008$). The warfarin group in paired within-group comparisons had significantly greater improvements in total bilirubin and albumin levels at baseline versus at 6 months postoperatively and in creatinine levels at baseline versus at 12, 18, and 24 months postoperatively respectively (all $P < 0.05$). In contrast, those paired comparisons of the aspirin group showed no significant differences (all $P > 0.05$).

Conclusions: Warfarin therapy was safe and effective and significantly reduced the risk of PVST after LSD, compared with aspirin treatment. Warfarin treatment was associated with better liver function protection and renal function improvement than aspirin treatment.

1. Introduction

Portal vein system thrombosis (PVST) is a common, potentially life-threatening complication after splenectomy, including open or laparoscopic splenectomy [1–3] and open or laparoscopic splenectomy and azygoportal disconnection (LSD), in patients with cirrhotic portal hypertension [3–7].

The reported incidence of PVST after laparoscopic splenectomy for various spleen disorders ranges from 42.9% to 55% [3,8–10]. The reported incidence of PVST in patients with cirrhotic portal hypertension ranges from 24.0% to 29.0% after open splenectomy (OS) [1,2], from 30.1% to 47.8% after open splenectomy and azygoportal disconnection (OSD) [3,4], and from 50% to 64% after LSD [5,6].

PVST may result in deterioration of the clinical course [11], causing liver function damage, increased risk of variceal bleeding resulting from portal hypertension, and ischemic intestinal necrosis [12–16]. Furthermore, PVST may reduce the possibility of future liver transplantation [17,18] and increases post-transplant mortality [19,20]. A previous study reported a 10-year survival among adults with PVST of 38%–60%; the reported mortality resulting from variceal bleeding in patients with PVST with cirrhosis is 30%–70% [21].

To date, no randomized prospective studies have focused on PVST prevention. The optimal recognized anticoagulation drugs for effectively and safely preventing PVST in cirrhotic patients after LSD for

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portal hypertensive bleeding and secondary hypersplenism remain unclear. The most common oral antiplatelet agents include aspirin, dipyridamole, and clopidogrel bisulfate, all of which are regarded as having little effect in postoperative PVST prophylaxis. While the most common oral anticoagulation drug is warfarin, which was comparatively very inexpensive and seldom reported to prevent PVST after LSD. Thus, we designed a pragmatic, nonprofit, randomized controlled trial to compare the safety and efficacy of warfarin versus aspirin in cirrhotic patients after LSD, with the primary endpoint of PVST prevention. Secondary endpoints were prevention of liver decompensation and esophageal variceal rebleeding, changes in liver and renal function, development of hepatocellular carcinoma, and overall survival.

2. Materials and methods

2.1. Participants

Between September 2014 and September 2017, all consecutive patients admitted at the Department of Hepatobiliary Surgery who satisfied predefined inclusion criteria were recruited. Eligible patients were ≥18 years of age and had a clinical, radiological, or histologic diagnosis of cirrhosis of any etiology, a Child–Pugh score from A5 to B9, splenomegaly secondary to hypersplenism with platelet count $\leq 50 \times 10^9$/L, prior variceal hemorrhage, no evidence of PVST on ultrasound evaluation or angio-computed tomography (CT), and informed consent to participate in the study. Before enrollment, all patients underwent hepatic, renal, and coagulation evaluations.

Exclusion criteria were age > 75 years; hepatocellular carcinoma or any other malignancy; chronic renal failure; thromboembolic disease (deep venous thrombosis, pulmonary embolism, etc); hypercoagulable state other than related to liver disease (nephrotic syndrome, malignancy, pregnancy, etc); ongoing drug treatment, including oral contraceptives, anticoagulants, and antiplatelet drugs; baseline INR > 2; recent peptic ulcer disease; history of hemorrhagic stroke; uncontrolled hypertension; pregnancy; human immunodeficiency virus infection; conversion to laparotomy; and declined to participate.

All patients underwent LSD with intraoperative autologous cell salvage. All operations were performed by the same surgical team. The surgical procedure is described in our previous reports [22,23]. The study was conducted according to the guidelines of the Declaration of Helsinki and the applicable provisions of good clinical practice in clinical trials. All authors had access to the study data and reviewed and approved the final manuscript.

2.2. Study design

The experimental arm of this study received oral administration of warfarin sodium (SINE, Shanghai, China) for 1 year beginning on postoperative day (POD) 3 at an initial dose of 2.5 mg/day, with dose adjustments to reach a target international normalized ratio (INR) of 2–3. Then, if PVST occurred during the first year, a target INR of 2–3 was maintained by adjusting the dose of warfarin. Otherwise, the previous dose of warfarin was kept, regardless of whether the postoperative INR level was gradually improved. In addition, if PVST occurred during the second year, warfarin was administered again, with a target INR of 2–3. Once PVST resolved, warfarin was discontinued. On the other hand, if PVST did not occur during the second year, warfarin was not administered. The control arm received 100-mg enteric-coated aspirin tablets (Bayer, Leverkusen, Germany) once daily for 1 year. If PVST occurred during the second year, aspirin therapy was restarted. Beginning on POD 3, both groups received low-molecular-weight heparin (CS Bio, Hebei, China) subcutaneously (4.100 IU/day) for 5 days and 25 mg of oral dipyridamole (Henan Furen, Henan, China) three times daily for 3 months. All patients were followed for 2 years.

Patients were randomized to two arms by an independent statistician who prepared sequentially numbered, opaque, sealed envelopes with a concealed block size of 10 derived from a computer-generated scheme. Patients who met the inclusion criteria had an equal probability, with random assignment, to be assigned to either treatment arm. Patients and their caregivers were masked to treatment assignments. Sonographers and radiologists who assessed the primary outcome with ultrasound and angio-CT, respectively, were blinded to arm assignment. Electronic gastroscopy examination was performed every 3 months during the follow-up period. If the diameter of esophageal varices was greater than 5 mm, variceal ligation was performed. If rebleeding happened during the follow-up period, urgent electronic gastroscopy was performed. If ascites was present at admission, surgery was not performed until ascites resolved with diuretics.

2.3. Efficacy assessment

The primary endpoint of the study was 2-year prevention of PVST, defined as development of portal vein thrombosis, splenic vein thrombosis, and/or mesenteric vein thrombosis. Ultrasound evaluation of the portal vein system was performed at baseline, on POD 7, at postoperative months (POM) 1 and 3, and every 3 months thereafter. The portal vein system was examined with angio-CT at enrollment and at months 3, 9, 15, and 21 after surgery. Whenever there was a suspected thrombotic event on ultrasound evaluation, angio-CT was repeated to make an assessment. Secondary endpoints were: 1) occurrence or recurrence of liver decompensation, defined as development of ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, or portal hypertensive bleeding; 2) changes in liver or renal function; and 3) hepatocellular carcinoma and overall survival.

Patients received regular outpatient clinical reexamination every 3 months, unless clinical conditions required endoscopic intervention or other clinical treatment. Patients who quit the treatment plan or discontinued drugs because of side effects or subjective rejection were regarded as withdrawing from the study. All other patients were followed until death or completion of the 2-year follow-up period. Results were analyzed according to intention to treat. Reporting of this randomized controlled trial was performed according to criteria in the most recent CONSORT statement [24].

2.4. Safety assessment

All side effects were recorded according to the World Health Organization toxicity grading system [25]. Protocol guidelines allowed for dose interruption in patients who had important laboratory value abnormalities or relevant adverse events. If these problems resolved, the drug was resumed; otherwise, therapy was terminated.

2.5. Statistical analysis

PVST incidence was chosen as the primary outcome for sample size calculation. On the basis of our previous retrospective study that reported a 3-month main portal vein thrombosis (MPVT) incidence of 8.8% after LSD in the warfarin arm and 33.3% in the aspirin arm [26], we calculated that 34 patients needed to be recruited in each arm to demonstrate a statistically significant difference between treatment arms with 80% power at a level of significance of 0.10 [27].

Data are presented as mean ± standard deviation, median (range), or percentage, as appropriate. Group means were compared with Student's t-test (paired-samples Student's t-test when applicable) or the Mann–Whitney *U* test, as appropriate. Percentages were compared with the chi-squared test (Fisher's exact test when applicable). The incidence of PVST in the warfarin and aspirin groups during the 2-year postoperative period were compared with two-way repeated-measures analysis to determine the dynamic changes in the two groups over time. Values of $P < 0.05$ were considered statistically significant. All statistical tests were two-sided and were performed with SPSS 22.0 software (SPSS, Inc., Chicago, IL, USA).

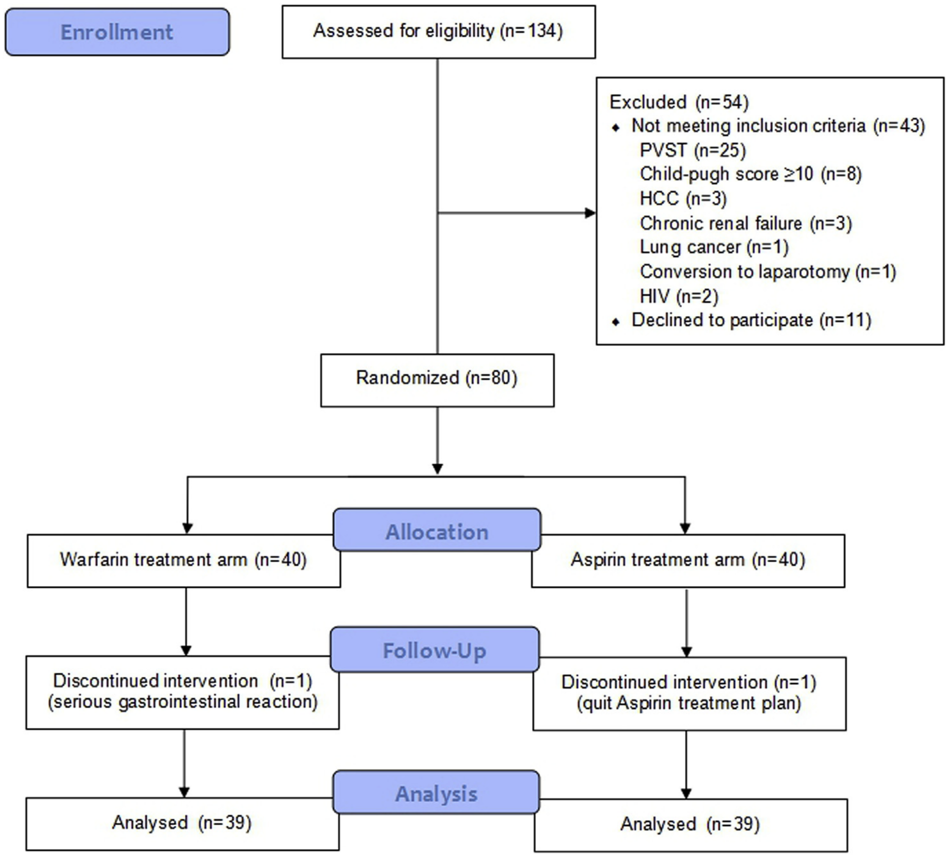

Fig. 1. CONSORT flow diagram for the study.
Abbreviations: PVST, portal vein system thrombosis; HCC, hepatocellular carcinoma; HIV, human immunodeficiency virus infection.

Role of funding source

This study was independently designed and was not supported by any pharmaceutical company. Patients bought relevant drugs themselves. This study abides by the rules of access to data, accountability, and control of publications of the International Committee of Medical Journal Editors [28].

3. Results

Fig. 1 presents the trial profile. A total of 134 patients with cirrhosis who had portal hypertensive bleeding and secondary hypersplenism were screened for study eligibility. Fifty-four patients were excluded; the remaining 80 patients were randomly assigned to the warfarin group (n = 40) or aspirin group (n = 40). None of the patients in either group underwent conversion to laparotomy. All patients but two completed the treatment. One patient withdrew because of serious gastrointestinal reaction to warfarin on POD 3; the second patient discontinued aspirin treatment on POD 5. The study was completed as planned in September 2017. There were no missing values for the primary outcome.

There were no significant differences in demographics, baseline characteristics, or intraoperative clinical characteristics between the two groups (all $P > 0.05$; Table 1). The overall incidence of PVST was 75.6% (59/78); 11.9% of these patients (7/59) were symptomatic (2/25 [8.0%] in warfarin group vs. 5/34 [14.7%] in aspirin group; $P = 0.704$]. Symptoms of PVST were nonspecific abdominal pain in four patients (one in warfarin group, three in aspirin group), fever in two patients (one in each group), and abdominal pain associated with fever in one patient (aspirin group). All symptoms resolved over time. All patients were discharged in good condition. Three patients (two in

Table 1
The baseline and intraoperative clinical characteristics of warfarin and aspirin groups.

Variable	Warfarin (n = 39)	Aspirin (n = 39)	P
Gender (female/male)	15/24	12/27	0.475
Age (years)	52.2 ± 10.4	50.5 ± 8.3	0.450
Etiology (1/2/3/4/5/6[a])	28/3/1/0/3/4	33/2/0/1/1/2	0.403
Hypertension	3	5	0.709
Diabetes	6	8	0.555
BMI	23.55 ± 2.65	24.03 ± 2.94	0.446
Child–Pugh score	5.9 ± 1.0	6.1 ± 1.0	0.419
INR	1.34 ± 0.15	1.37 ± 0.15	0.403
D-dimer (mg/L)	1.16 ± 1.11	1.83 ± 3.64	0.276
WBC ($\times 10^9$/L)	2.80 ± 1.98	2.41 ± 1.06	0.285
Hb ($\times 10^9$/L)	105.4 ± 26.8	104.7 ± 26.8	0.906
PLT ($\times 10^9$/L)	39.3 ± 8.9	39.4 ± 9.9	0.952
TBIL (umol/L)	21.57 ± 8.05	21.99 ± 8.20	0.520
ALB (g/L)	39.41 ± 5.28	39.23 ± 5.19	0.880
ALT (U/L)	28.87 ± 19.16	24.85 ± 14.07	0.294
BUN (mmol/L)	5.46 ± 2.37	5.42 ± 1.87	0.926
CRE (umol/L)	75.23 ± 21.91	76.03 ± 21.75	0.873
Longitudinal diameter of spleen (mm)	181.5 ± 25.0	185.9 ± 30.8	0.490
Portal vein diameter (mm)	13.4 ± 2.9	14.3 ± 2.3	0.122
Velocity of portal blood flow (cm/s)[b]	15.33 ± 5.50	17.03 ± 7.22	0.248
Duration of surgery (min)	161.5 ± 30.8	167.3 ± 38.0	0.465
Intraoperative blood loss (ml)	75.4 ± 84.7	83.8 ± 77.7	0.647

Data shown as mean ± standard deviation, or number of patients, as indicated. BMI, Body Mass Index; WBC, white blood cell; Hb, hemoglobin; PLT, platelets; ALT, Alanine transaminase; BUN, blood urea nitrogen; CRE, creatinine.
[a] 1/2/3/4/5/6, Hepatitis B/hepatitis C/schistosomiasis/alcohol/autoimmunity/idiopathic cirrhosis.
[b] Preoperative velocity of portal blood flow.

warfarin group, one in aspirin group) died during follow-up. All other patients finished the 2-year follow-up as planned.

3.1. Platelet level

There were no significant differences in platelet counts between the warfarin and aspirin groups at 6 months ([248.7 ± 118.6] × 10^9/L vs. [237.4 ± 93.9] × 10^9/L), 12 months ([239.7 ± 90.7] × 10^9/L vs. [220.9 ± 97.6] × 10^9/L), 18 months ([221.2 ± 78.1] × 10^9/L vs. [203.9 ± 89.8] × 10^9/L), or 24 months ([208.5 ± 69.4] × 10^9/L vs. [200.7 ± 84.3] × 10^9/L) (all $P > 0.05$).

3.2. Dose of warfarin sodium

According to study design, warfarin-treated patients needed to take oral warfarin at a dose of 3.702 ± 0.231 mg daily to reach the target INR of 2–3 in the incipient stage. The daily dose of oral warfarin was 3.799 ± 0.234 mg at POM 3, 3.832 ± 0.238 mg at POM 6, 3.849 ± 0.240 mg at POM 9, and 3.849 ± 0.240 mg at POM 12. The median dose was 3.750 mg and the dose range was 1.875–7.500 mg at all time points.

3.3. Incidence of PVST

The incidence of PVST in the first 2 postoperative years was significantly lower in the warfarin group than in the aspirin group (F = 7.360, $P = 0.008$; Fig. 2). During the first year of active treatment, 15 of the warfarin-treated patients (15/39, 38.5%) did not develop PVST, compared with five of 39 (12.8%) aspirin-treated patients ($P = 0.010$). During the entire 2-year period, 14 patients in the warfarin group (14/39, 35.9%) did not develop PVST, compared with five (12.8%) in the aspirin group ($P = 0.018$). During the second year of follow-up, 33 warfarin-treated patients (33/38, 86.8%) did not develop PVST, compared with 33 of 38 (86.8%) aspirin-treated patients

Table 2
The comparison of thrombosis incidence between warfarin and aspirin groups.

Variable	Warfarin	Aspirin	P
PVST			
POD 7	19 (n = 39, 48.7%)	23 (n = 39, 59.0%)	0.364
POM 1	18 (n = 39, 46.2%)	23 (n = 38, 60.5%)	0.206
POM 3	8 (n = 38, 21.1%)	23 (n = 38, 60.5%)	< 0.001
POM 6	4 (n = 38, 10.5%)	14 (n = 38, 36.8%)	0.007
POM 9	3 (n = 38, 7.9%)	8 (n = 38, 21.1%)	0.103
POM 12	1 (n = 38, 2.6%)	2 (n = 38, 5.3%)	1.000
POM 15	3 (n = 38, 7.9%)	3 (n = 38, 7.9%)	1.000
POM 18	3 (n = 38, 7.9%)	5 (n = 38, 13.2%)	0.709
POM 21	1 (n = 37, 2.7%)	5 (n = 38, 13.2%)	0.214
POM 24	0 (n = 37, 0.0%)	4 (n = 38, 10.5%)	0.130
MIPVT			
POD 7	12 (n = 39, 30.8%)	10 (n = 39, 25.6%)	0.615
POM 1	9 (n = 39, 23.7%)	13 (n = 38, 34.2%)	0.312
POM 3	5 (n = 38, 13.2%)	15 (n = 38, 39.5%)	0.009
POM 6	2 (n = 38, 5.3%)	12 (n = 38, 31.6%)	0.003
POM 9	2 (n = 38, 5.3%)	6 (n = 38, 15.8%)	0.262
POM12	0 (n = 38, 0.0%)	2 (n = 38, 5.3%)	0.474
POM 15	0 (n = 38, 0.0%)	3 (n = 38, 7.9%)	0.239
POM 18	2 (n = 38, 5.3%)	5 (n = 38, 13.2%)	0.428
POM 21	1 (n = 37, 2.7%)	5 (n = 38, 13.2%)	0.214
POM 24	0 (n = 37, 0.0%)	5 (n = 38, 13.2%)	0.069
SVT			
POD 7	13 (n = 39, 33.3%)	20 (n = 39, 51.3%)	0.109
POM 1	10 (n = 39, 25.6%)	20 (n = 39, 51.3%)	0.015
POM 3	6 (n = 38, 15.8%)	18 (n = 38, 47.4%)	0.003
POM 6	2 (n = 38, 5.3%)	4 (n = 38, 10.5%)	0.671
POM 9	2 (n = 38, 5.3%)	4 (n = 38, 10.5%)	0.671
POM 12	1 (n = 38, 2.6%)	0 (n = 38, 0.0%)	1.000
POM 15	2 (n = 38, 5.3%)	0 (n = 38, 0.0%)	0.474
POM 18	1 (n = 38, 2.6%)	1 (n = 38, 2.6%)	1.000
POM 21	0 (n = 37, 0.0%)	1 (n = 38, 2.6%)	1.000
POM 24	0 (n = 37, 0.0%)	1 (n = 38, 2.6%)	1.000

Data shown as number of patients (percentage), as indicated.
SVT, splenic vein thrombosis.

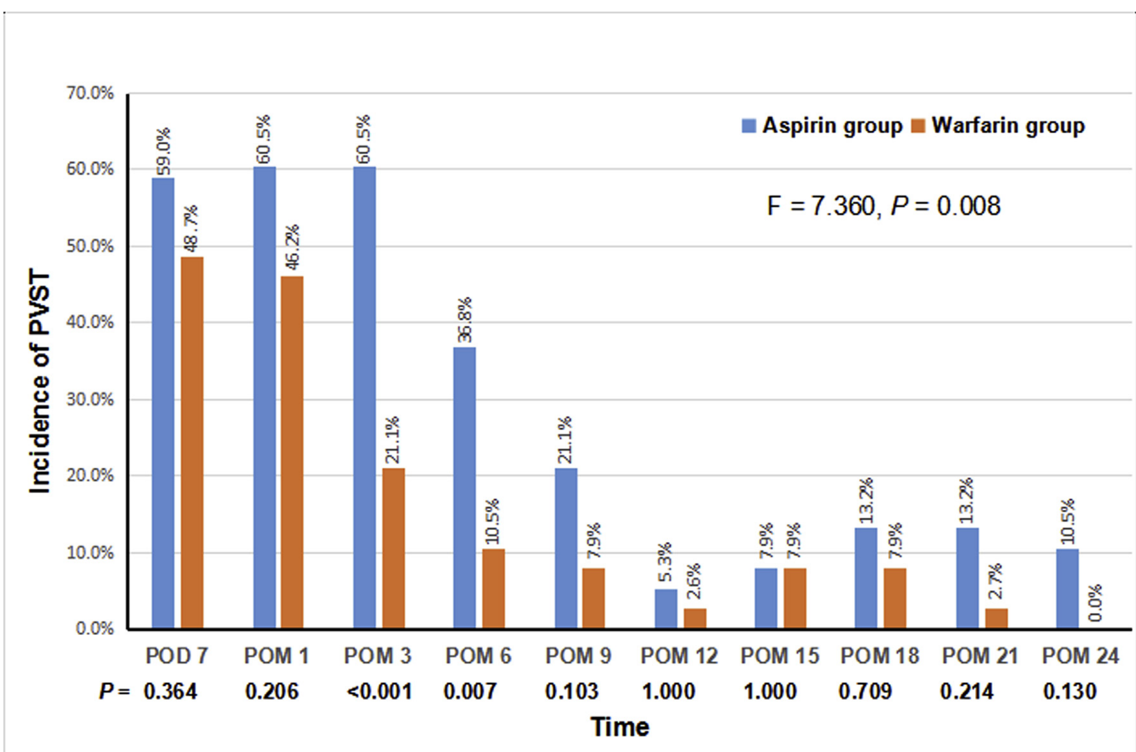

Fig. 2. Dynamic changes in the incidence of PVST in the warfarin and aspirin groups (F = 7.360, $P = 0.008$).; Abbreviations: PVST, portal vein system thrombosis; POD, postoperative day; POM, postoperative month.

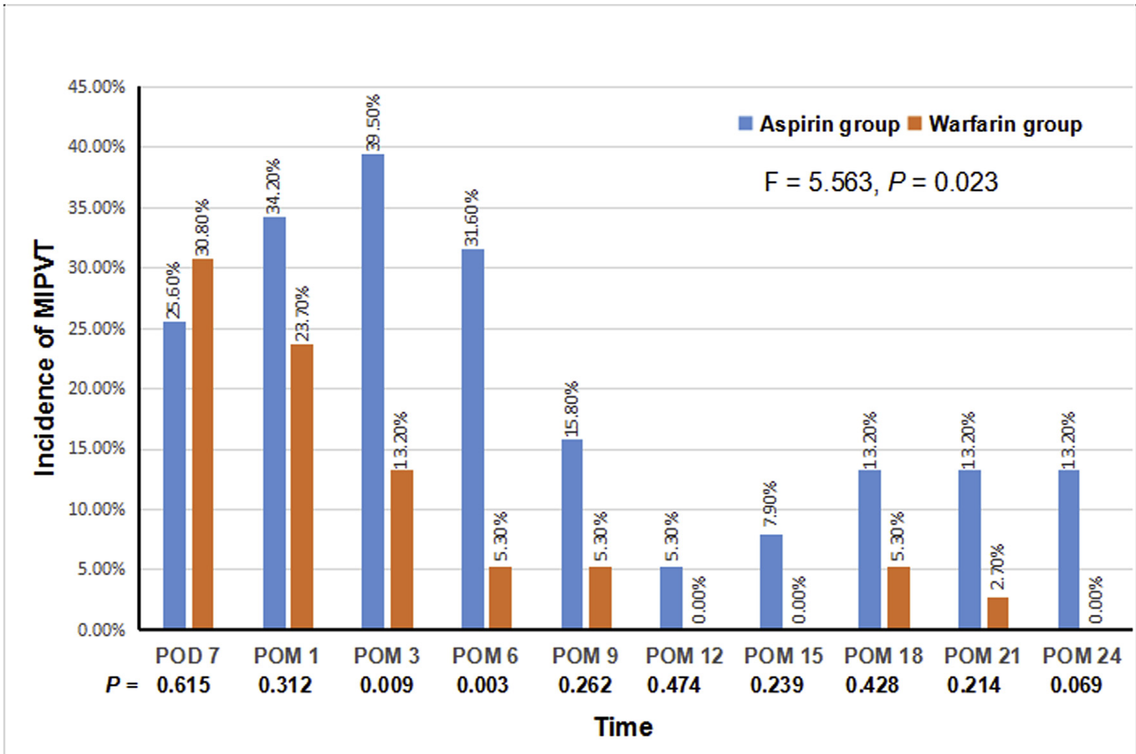

Fig. 3. Dynamic changes in the incidence of MIPVT in the warfarin and aspirin groups (F = 5.365, $P = 0.023$).; Abbreviations: MIPVT, main and intrahepatic branches of portal vein thrombosis; POD, postoperative day; POM, postoperative month.

($P = 1.000$). Because of PVST occurrence 12 months postoperatively or during the second year, five patients in the warfarin group (5/38, 13.5%) continued or resumed their previous warfarin treatment and six of 38 patients (15.8%) continued or resumed aspirin treatment ($P > 0.05$).

There were no significant differences between the groups in PVST incidence on POD 7 or at POM 1 (both $P > 0.05$; Table 2). However, at 3 and 6 months postoperatively, the PVST incidence was significantly lower in the warfarin group than in the aspirin group ($P < 0.0001$ and $P = 0.007$, respectively; Table 2). At later time points (9, 12, 15, 18, 21, and 24 months postoperatively) there were no significant differences in PVST incidence between the groups (all $P > 0.05$; Table 2, Fig. 2).

Incidence of Main and Intrahepatic Branches of Portal Vein Thrombosis (MIPVT).

The incidence of MIPVT in the first 2 postoperative years was significantly lower in the warfarin group than in the aspirin group (F = 5.365, $P = 0.023$; Fig. 3). There were no significant differences in the incidence of MIPVT on POD 7 or at POM 1 (both $P > 0.05$; Table 2). However, at POM 3 and 6, the incidence of MIPVT was significantly lower in the warfarin group than in the aspirin group (P = 0.009 and $P = 0.003$, respectively; Table 2). The incidence of MIPVT was similar between the groups at POM 9, 12, 15, 18, 21, and 24 (all $P > 0.05$; Table 2, Fig. 2).

3.4. Incidence of splenic vein thrombosis

The incidence of splenic vein thrombosis in the first 2 postoperative years was significantly lower in the warfarin group than in the aspirin group (F = 5.563, $P = 0.021$). There was no significant difference between the groups in the incidence of splenic vein thrombosis on POD 7 ($P > 0.05$; Table 2). However, at POM 1 and 3, the incidence of splenic vein thrombosis was significantly lower in the warfarin group than in the aspirin group ($P = 0.015$ and $P = 0.003$, respectively; Table 2). The incidence of splenic vein thrombosis at POM 6, 9, 12, 15, 18, 21, and 24 was similar between the two groups (all $P > 0.05$; Table 2).

3.5. Incidence of mesenteric vein thrombosis

Among all patients in the two groups, only one (in warfarin group) developed asymptomatic superior mesenteric vein thrombosis during the 2-year follow-up period. In that patient, the thrombosis was found on POD 7 and resolved by POM 1. There was no significant difference between the groups in the incidence of mesenteric vein thrombosis during the 2-year period (0/38 in aspirin group vs 1/37 in warfarin group; $P > 0.05$). The patient who discontinued aspirin treatment was readmitted at POM 18 because of abdominal pain with massive ascites, main and left-branch portal vein thrombosis, superior mesenteric vein thrombosis, and extensive colon wall edema. That patient ultimately died.

3.6. Occurrence of decompensation

During the first year, including during the first and second 6-month periods and during the whole year, liver decompensation developed at similar rates between the two groups (all $P > 0.05$; Table 3). During the second year, the occurrence of decompensation was also similar between the groups ($P > 0.05$; Table 3). There were no significant differences between the groups in the occurrence of decompensation at POM 6, 12, 18, or 24 (all $P > 0.05$; Table 3). Ascites was the most frequent event; its incidence was similar between the groups at POM 6, 12, 18, and 24 (all $P > 0.05$; Table 3). The incidence of variceal bleeding and liver encephalopathy were identical between the groups (four patients and one patient in each group, respectively) during the 2 years (all $P = 1.000$). No cases of spontaneous bacterial peritonitis occurred in either group.

Table 3
Incidence of liver decompensation and ascites in warfarin and aspirin groups.

Variable	Warfarin	Aspirin	P
LD			
POM 6	10 (n = 38, 26.3%)	8 (n = 38, 21.1%)	0.589
POM 12	8 (n = 38, 21.1%)	9 (n = 38, 23.7%)	0.783
POM 18	10 (n = 38, 26.3%)	5 (n = 38, 13.2%)	0.150
POM 24	7 (n = 37, 18.9%)	5 (n = 38, 13.2%)	0.496
POM 1–6	13 (n = 38, 69.2%)	28 (n = 38, 71.8%)	0.804
POM 7–12	13 (n = 38, 34.2%)	12 (n = 38, 31.6%)	0.807
POM 1–12	32 (n = 38, 82.1%)	30 (n = 38, 76.9%)	0.575
POM13–24	15 (n = 38, 39.5%)	10 (n = 38, 26.3%)	0.222
Ascites			
POM 6	10 (n = 38, 26.3%)	8 (n = 38, 21.1%)	0.589
POM 12	8 (n = 38, 21.1%)	9 (n = 38, 23.7%)	0.783
POM 18	10 (n = 38, 26.3%)	5 (n = 38, 13.2%)	0.150
POM 24	7 (n = 37, 18.9%)	5 (n = 38, 13.2%)	0.496
POM 1–6	27 (n = 38, 69.2%)	28 (n = 38, 71.8%)	0.804
POM 7–12	11 (n = 38, 28.9%)	11 (n = 38, 28.9%)	1.000
POM 1–12	29 (n = 38, 74.4%)	29 (n = 38, 74.4%)	1.000
POM 13–24	13 (n = 38, 34.2%)	11 (n = 38, 28.9%)	0.622

Data shown as number of patients (percentage), or mean ± standard deviation, as indicated.
LD, liver decompensation.
POM 1–6: from POD 1 to the last day of POM 6.
POM 7–12: from the first day of POM 7 to the last day of POM 12.
POM 1–12: from POD 1 to the last day of POM 12.
POM 13–24: from the first day of POM 13 to the last day of POM 24.

3.7. Effect on INR

Paired within-group comparisons of INR at POM 6, 12, 18, and 24 versus at baseline in the aspirin group all showed significantly lower INR (all $P < 0.001$; Table 4). However, because of active warfarin treatment in the first year, INR in the warfarin group at POM 6 was higher than at baseline ($P < 0.001$; Table 4) and INR at POM 12 was similar to INR at baseline ($P = 0.854$). After discontinuation of active treatment in the second year, INR levels were significantly improved at POM 18 and 24, compared with baseline (excluding four patients who continued warfarin treatment; all $P < 0.001$; Table 4).

3.8. Effect on Child-Pugh scores

Paired comparisons of Child-Pugh scores in aspirin-treated patients at baseline versus at POM 6, 12, 18, and 24 showed significant improvements in Child–Pugh score at each time point (all $P < 0.01$; Table 4). In warfarin-treated patients, Child–Pugh scores were not analyzed during the first year because of prolonged prothrombin time resulting from active warfarin treatment. During the second year, after discontinuation of active treatment, Child-Pugh scores significantly improved from baseline to POM 18 and POM 24, excluding four patients who continued warfarin treatment (three patients at POM 18 and one at POM 24) (all $P < 0.001$; Table 4).

3.9. Effect on liver function

Paired within-group comparisons of liver function [total bilirubin (TBIL), albumin (ALB)] at baseline versus at POM 6, 12, 18, and 24 showed significant improvement in liver function among warfarin-treated patients at each time point (all $P < 0.01$). In contrast, paired comparisons in the aspirin-treated group showed no significant differences in liver function between baseline and POM 6 (both $P > 0.05$; Table 4).

3.10. Effects on renal function

Paired within-group comparisons of renal function [creatinine (CRE)] at baseline versus at POM 12, 18, and 24 showed significant improvement in renal function among warfarin-treated patients beginning at POM 12 through POM 24 (all $P < 0.05$). In contrast, paired comparisons among aspirin-treated patients showed no significant improvement in renal function from baseline to any time point (all $P > 0.05$; Table 4).

3.11. Survival

Two patients in the warfarin group and one in the aspirin group died ($P = 1.000$). Causes of death were gastroesophageal variceal bleeding (one patient in warfarin group died on POD 23, one in aspirin group died on POD 45) and unknown cause (one in warfarin group died on POM 19).

3.12. Safety

Aspirin treatment was very well tolerated. In the warfarin group, one patient stopped treatment because of a serious gastrointestinal

Table 4
Markers of liver disease severity (INR, Child-Pugh score, ALB, TBIL) and creatinine levels (CRE) in warfarin and aspirin groups.

	INR	P	Child–Pugh score	P	TBIL (umol/L)	P	ALB (g/L)	P	CRE (umol/L)	P
Warfarin group										
(N = 38) Baseline	1.34 ± 0.16	< 0.001	NA	NA	21.62 ± 8.14	< 0.001	39.48 ± 5.33	< 0.001	75.68 ± 22.02	0.096
POM 6	1.71 ± 0.48		NA		15.22 ± 6.24		44.67 ± 4.61		71.87 ± 14.79	
(N = 38) Baseline	1.34 ± 0.16	0.854	NA	NA	21.62 ± 8.14	0.006	39.48 ± 5.33	< 0.001	75.68 ± 22.02	0.002
POM 12	1.35 ± 0.28		NA		16.93 ± 9.12		45.76 ± 5.24		68.29 ± 16.33	
(N = 38) Baseline	1.34 ± 0.16	< 0.001[a]	5.9 ± 1.0	< 0.001[a]	21.62 ± 8.14	0.009	39.48 ± 5.33	< 0.001	75.68 ± 22.02	0.021
POM 18	1.09 ± 0.09		5.2 ± 0.5		17.27 ± 9.69		45.77 ± 5.36		69.47 ± 16.97	
(N = 37) Baseline	1.34 ± 0.16	< 0.001[b]	5.9 ± 1.0	< 0.001[b]	21.54 ± 8.24	0.001	39.56 ± 5.38	< 0.001	75.57 ± 22.31	0.013
POM 24	1.10 ± 0.11		5.1 ± 0.3		16.52 ± 5.99		46.23 ± 6.05		70.03 ± 15.94	
Aspirin group										
(N = 38) Baseline	1.37 ± 0.15	< 0.001	6.1 ± 1.0	0.001	22.15 ± 8.26	0.109	39.09 ± 5.18	0.138	75.95 ± 22.03	0.321
POM 6	1.15 ± 0.12		5.4 ± 0.7		20.11 ± 5.98		40.51 ± 4.03		73.47 ± 17.99	
(N = 38) Baseline	1.37 ± 0.15	< 0.001	6.1 ± 1.0	< 0.001	22.15 ± 8.26	0.024	39.09 ± 5.18	< 0.001	75.95 ± 22.03	0.849
POM 12	1.10 ± 0.09		5.3 ± 0.6		18.55 ± 6.38		45.01 ± 5.29		75.55 ± 14.82	
(N = 38) Baseline	1.37 ± 0.15	< 0.001	6.1 ± 1.0	< 0.001	22.15 ± 8.26	0.003	39.09 ± 5.18	< 0.001	75.95 ± 22.03	0.587
POM 18	1.09 ± 0.07		5.3 ± 0.5		18.09 ± 6.05		45.53 ± 3.49		74.71 ± 15.54	
(N = 38) Baseline	1.37 ± 0.15	< 0.001	6.1 ± 1.0	< 0.001	22.15 ± 8.26	0.005	39.09 ± 5.18	< 0.001	75.95 ± 22.03	0.504
POM 24	1.08 ± 0.07		5.2 ± 0.4		18.26 ± 6.07		46.17 ± 3.59		74.44 ± 17.23	

Data shown as mean ± standard deviation, as indicated.
[a] Excluding three patients on ongoing oral warfarin.
[b] Excluding one patient on ongoing oral warfarin.

reaction involving nausea and vomiting on POD 3. Because of abnormal INR levels ≥3.0, five patients suspended warfarin treatment for 1–2 days until INR levels were less than 2.0. Two patients had drug resistance, with INR levels persistently below 2.0 despite an oral warfarin dose of 7.5 mg/day; these two patients continued taking 7.5 mg/day until the end of the 1-year treatment. There were no significant between-group differences in the incidence of gastroesophageal variceal bleeding (four in each group; $P = 1.000$), hepatic encephalopathy (one in each group; $P = 1.000$), or hepatocellular carcinoma (one in warfarin group, two in aspirin group; $P = 1.000$).

4. Discussion

To date, there is no standard, recognized anticoagulation treatment protocol for the prevention of postoperative PVST after splenectomy in patients with cirrhotic portal hypertension. PVST can progress to fibrosis, making drug-induced thrombolysis difficult. Furthermore, severe splenic vein thrombosis may progress to portal vein thrombosis [29] or even disastrous superior mesenteric vein thrombosis [30]. Therefore, PVST should be prevented with a safe and effective anticoagulation agent.

The mechanism by which LSD/LS contributes to a higher rate of PVST than OSD/OS is not yet clear [3–6,8–10]. Some factors that may contribute to the formation of PVST include CO2 pneumoperitoneum, the technique used for splenic vessel ligation (stapled vascular transection en masse), and use of the LigaSure vessel-sealing device (Covidien, Boulder, CO) or harmonic shears (Ethicon, Cincinnati, OH), both of which may lead to venous intimal damage by heat energy or oscillation. The effects on the vessels and tissues by these processes may be potential factors that contribute to PVST. In addition, LSD is preferable to OSD, with many advantages including minimal surgical trauma, lower inflammatory immune responses, fewer postoperative complications, and more fast recovery [6,22,31].

Clinical studies on the use of warfarin to prevent portal vein thrombosis after splenectomy for cirrhotic portal hypertension are scarce. The results of this 2-year randomized controlled trial in a cohort of cirrhotic portal hypertension patients who underwent LSD for gastroesophageal variceal bleeding and secondary hypersplenism showed that anticoagulant treatment with warfarin was safe and effective. Warfarin treatment significantly reduced the risk of postoperative PVST development, prevented liver damage, improved renal function, and markedly improved TBIL, ALB, and CRE levels, compared with aspirin treatment. To our knowledge, this is the first randomized controlled trial focusing on PVST prevention to draw these conclusions. Few retrospective studies have assessed the postoperative incidence of PVST beyond 3 months after splenectomy.

This study showed the incidence of PVST in the warfarin group at POM 3, 6, and 9 were all approximately one-third the incidence in the aspirin group at the same time points. For long-term prevention in the second year, warfarin treatment more effectively dissolved recurrent or stubborn thrombosis than aspirin, with none showing thrombosis of the main or intrahepatic branches of the portal vein. In contrast, five patients in the aspirin group had thrombosis of the main or intrahepatic branches of the portal vein at the end of the second year. Notably, this difference between the groups was not significant ($P = 0.068$), presumably because of the small sample size.

Postoperation liver function (TBIL and ALB) gradually improved over time in both treatment groups in this study. The paired comparisons in the aspirin-treated group showed no significant differences in liver function between baseline and POM 6. In contrast, that had significant differences in the warfarin-treated group. This difference could be attributed to a lower PVST incidence at POM 3 and POM 6 in the warfarin group. It is reasonable that PVST obstruction decreases blood volume to the liver and increases liver damage.

A previous randomized controlled trial reported that low-molecular-weight heparin (Enoxaparin) was safe and effective in preventing PVST in patients with advanced cirrhosis [32]. In that study, patients received low-molecular-weight heparin subcutaneously at a prophylactic dose (4000 IU/day) for 48 weeks. Obviously, that method not only requires a high level of compliance from patients, who must undergo 336 subcutaneous injections, but it is also an expensive approach. Warfarin is comparatively very inexpensive and requires only low-level compliance.

There is little information on the appropriate dose of oral warfarin for cirrhotic patients with portal hypertension after splenectomy. Some surgeons worry about the bleeding caused by warfarin treatment for cirrhotic patients with coagulation disorders, especially during the perioperative period. This study showed that coagulation function gradually improved after LSD and that warfarin treatment was safe at a median dose of 3.750 mg over time; the mean warfarin dose was gradually increased from 3.702 mg to 3.849 mg during the first year of active treatment.

A prior retrospective observational study also found that warfarin therapy with a target INR of 2–3 over 18 months delayed renal function deterioration in elderly patients with chronic kidney disease better than aspirin regimens (100 mg/day) [33]. The findings of this study supported their conclusion about renal function. Notably, in the warfarin group, the CRE level gradually improved over the first year of active warfarin treatment; in the second year when treatment was not active, the CRE level increased over time. These changes that accompanied the use or discontinuation of oral warfarin suggest that warfarin treatment may be associated with improved renal function.

The main limitation of this study is its relatively small sample size. Another methodological question is the potentially limited external validity of the results for different populations and settings. Our study included a cohort of Chinese patients enrolled at a tertiary care center who had portal hypertensive bleeding and hypersplenism secondary to cirrhosis arising from different etiologies. In addition, the potential difficulty with clinical application of warfarin other than aspirin is that it sometimes seems a bit troublesome thing for adjusting the target INR.

The 2-year randomized controlled trial showed that anticoagulation therapy with warfarin beginning on postoperative day (POD) 3 at an initial dose of 2.5 mg/day, with dose adjustments to reach a target INR of 2–3 was safe and effective. Warfarin treatment significantly reduced the risk of postoperative PVST development after LSD, was associated with clear protection of liver function and improvement in renal function, and had favorable effects that were much greater than simply preventing PVST.

Ethical approval

The study protocol was approved by the Ethics Committee of the Clinical Medical College of Yangzhou University. The reference number is No. 2014014.

Conflicts of interest

We have no conflicts of interest to state.

Trial registry number

We registered our research at https://www.clinicaltrials.gov/. The name of research registered is"Warfarin Prevents Portal Vein Thrombosis in Patients After Laparoscopic Splenectomy and Azygoportal Disconnection ". The trial registration identifier at clinicaltrials.gov is NCT02247414.

Guarantor

Prof. Guo-Qing Jiang is the Guarantor.

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Data statement

The authors do not have permission to share data.

CRediT authorship contribution statement

Dou-Sheng Bai: Conceptualization, Data curation, Supervision, Writing - original draft. **Bing-Lan Xia:** Conceptualization, Formal analysis, Writing - original draft, Supervision. **Chi Zhang:** Conceptualization, Formal analysis, Writing - review & editing. **Jing Ye:** Investigation, Methodology, Project administration. **Jian-Jun Qian:** Data curation, Resources, Software. **Sheng-Jie Jin:** Formal analysis, Validation, Visualization. **Guo-Qing Jiang:** Conceptualization, Supervision, Formal analysis, Funding acquisition, Writing - review & editing.

Abbreviations

PVST	portal vein system thrombosis
LSD	laparoscopic splenectomy and azygoportal disconnection
OS	open splenectomy
OSD	open splenectomy and azygoportal disconnection
CT	computed tomography
POD	postoperative day
INR	normalized ratio
POM	postoperative months
MPVT	main portal vein thrombosis
MIPVT	main and intrahepatic branches of portal vein thrombosis
TBIL	bilirubin
ALB	albumin
CRE	creatinine.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijsu.2019.02.018.

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