

The postoperative splenic/portal vein thrombosis after splenectomy and its prevention – an unresolved issue

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ABSTRACT

Patients undergoing splenectomy have an increased risk of splenic/portal vein thrombosis. We used several databases to identify publications dealing with this risk and analyzed incidence, risk factors and outcome. The risk of splenic portal vein thrombosis has been addressed in prospective and retrospective randomized or non-randomized studies. All studies combined, the overall risk is 3.3%. Risk factors are big spleens (i.e. myeloproliferative disorders) and hereditary hemolytic anemias, whereas the risk is low in autoimmune thrombocytopenia and trauma. The incidence is approximately the same in laparoscopic and open splenectomy. The median time from splenectomy to symptomatic splenic vein thrombosis is 8–12 days. Postoperative antithrombotic prophylaxis ranged from no prophylaxis to heparin for seven days or longer. Treatment of symptomatic splenic vein thrombosis with heparin and warfarin leads to complete resolution of thrombosis in 67%, to partial resolution in 13%, but persistent occlusion, portal hypertension or cavernoma occurred in 20%. The long-term outcome of treatment failures is unknown. Well-designed randomized studies on the prophylaxis of venous thromboembolism after splenectomy are urgently needed.

Key words: portal vein thrombosis, risk factors, splenectomy, thromboembolism, treatment.

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Introduction

It is well known that surgery is associated with a risk for postoperative venous thromboembolism. Postoperative venous thrombosis occurs in most instances almost exclusively in deep veins of the lower extremities and may be asymptomatic (i.e. only detectable by phlebography, sonography) or symptomatic. Various risk categories have been defined based on preoperative individual patient risk factors and the type of surgery. Guidelines have been established on the necessity, intensity and duration of postoperative antithrombotic prophylaxis.¹

While the optimal postoperative antithrombotic management has been well defined² for most types of abdominal surgery, the postoperative risk and antithrombotic prophylaxis after splenectomy have not been studied systematically, although the risk may be considerable in some groups of patients.

Compared to other surgical interventions, the postoperative thrombotic risk in patients after splenectomy has some

specific features. The spleen obviously has an important function in the clearing of (yet undefined) prothrombotic factors, since removal of the spleen is associated with an elevated long-lasting thrombotic risk, even in patients without underlying disease (i.e. splenectomy because of trauma).^{3,4} Postoperative thrombocytosis is much more pronounced after splenectomy and may increase the thrombotic risk *per se*, although this has not yet been proven. The most important specific problem of splenectomy is that after this operation the patients are at risk for two different sites of thromboembolism – deep venous thrombosis (DVT) of the legs/pulmonary embolism (PE), as is the case after all surgical interventions, and additionally for splenic/portal vein thrombosis (SPVT), which is a specific thrombotic complication after splenectomy. These two types of thromboembolic events may have in common only some of the traditional prothrombotic risk factors.

Data on postoperative complications after splenectomy have been published mainly in surgical journals and in recent years concentrated on possible advantages of laparoscopic

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splenectomy. Only a few of these studies specifically addressed the problem of postoperative SPVT⁵⁻¹³ or DVT/PE.

In this paper we wish to analyze published systematic studies on postoperative SPVT and DVT/PE after splenectomy. Furthermore, we will analyze reports on individual cases or small series of cases with emphasis on incidence, risk factors, time interval from surgery to diagnosis of thrombosis, possible benefits of heparin prophylaxis, treatment of established SPVT and possible long-term sequelae. We will also suggest a practical prophylactic and therapeutic management on the basis of current knowledge.

Design and Methods

We searched for publications in various databases (Pubmed from 21st May 1949 to 26th February 2008, EMBASE from January 1974 to 26th February 2008). We used the search terms *portal vein thrombosis, splenic vein thrombosis, splenectomy, risk factors* and *treatment*. These search terms resemble our keywords and were combined with each other with and without "AND" function. We also used quoted references in papers on this topic. Manuscripts of all languages were reviewed.

Papers were evaluated independently by the authors MTK and KL. In case of disagreement the decision was made by the last author IP.

The studies were classified as randomized prospective studies, prospective cohort studies, retrospective studies and single case reports or small series of cases (<10 study patients).

Results

We identified only two randomized trials on postoperative thromboembolism after splenectomy. One study was a randomized prospective study that compared the incidence of asymptomatic and symptomatic SPVT after open (OS) and laparoscopic splenectomy (LS).⁸ Unfortunately, the two groups in this study were not balanced according to the underlying diseases, so the specific question of this study remained unanswered. However, the study is very informative as a cohort study. Another randomized study¹⁴ comparing OS and LS in thalassemia major did not evaluate the incidence of SPVT. Thus, only prospective or retrospective cohort studies, small series of cases and individual case reports could be used for the evaluation of the risk of SPVT and DVT/PE after splenectomy.

Incidence of asymptomatic and symptomatic splenic/portal vein thrombosis after splenectomy (Table 1 and 2)

The incidence of SPVT after splenectomy was evaluated prospectively with different imaging methods in ten studies, five after OS^{8-11,15} and five after LS.^{12,13,16,17,18} Contrast-enhanced computerized tomography (CT) was used by two studies of the same authors^{8,17} and color Doppler imaging in the remaining studies. The

time schedule for monitoring was not identical in these series and ranged from one single examination between days 3 and 11^{8,17} to two or more examinations (days 7, 30 and later).^{9,11,12} The patients were extremely heterogeneous with regard to the underlying diseases.

Overall, the total incidence of SPVT detected by imaging studies (asymptomatic or symptomatic) in prospective studies was 67/545 (12.3%) with a range of 4.8%-51.5%. The highest incidence (19.0%, 22.5% and 51.5%) was reported in the two prospective studies with CT monitoring^{8,17} and in one prospective study with color Doppler imaging at multiple time points.¹² In the CT studies small, often multiple thromboses (or emboli?) were discovered in various parts of splenic/portal veins. The incidence of symptomatic SPVT in these studies was 31/545 (5.7%) (range 0-19%). All in all, 31/67 (46.3%) of patients with positive imaging findings developed symptoms (fever, abdominal pain) which could be related to SPVT.

Table 1. Incidence of splenic/portal vein thrombosis after splenectomy in prospective studies (all adults).

Type of splenectomy	Patients (n)	SPVT+SVT all patients	Asymptomatic	Symptomatic	Ref.
Laparoscopic	40	9/40, (22.5%)	3/40, (7.5%)	6/40, (15%)	[12]
Laparoscopic	14	2/14, (14%)	2/14, (14%)	0	[13]
Laparoscopic	41	4/41, (9.8%)	4/41, (9.8%)	0	[16]
Laparoscopic	33	17/33, (51.5%)	13/33, (39.4%)	4/33, (12.1%)	[17]
Laparoscopic	20	2/20 (10%)	1/20 (5%)	1/20 (5%)	[18]
Laparoscopic all patients	148	34/148, (23%)	23/148, (15.5%)	11/148, (7.4%)	
Open	21	4/21, (19%) (all gastric cancer)	0	4/21, (19%)	[8]
Open	147	7/147, (4.8%)	2/147, (1.4%)	5/147, (3.4%)	[9]
Open	119	13/119, (10.9%)	7/119, (5.9%)	6/119, (5%)	[10]
Open	60	4/60, (6.7%)	3/60, (5%)	1/60, (1.7%)	[11]
Open	50	5/50, (10%)	1/50, (2%)	4/50, (8%)	[15]
Open all patients	397	33/397, (8.3%)	13/397, (3.3%)	20/397, (5%)	
Laparoscopic + open all patients	545	67/545 (12.3%)	36/545 (6.6%)	31/545 (5.7%)	

SPVT: splenic/portal vein thrombosis; SVT: splenic vein thrombosis; LS: laparoscopic splenectomy; OS: open splenectomy.

The incidence of only symptomatic SPVT was evaluated in eight retrospective cohort studies, three after OS¹⁹⁻²¹ and two after LS,^{22,23} in three other studies OS and LS were performed in the same study, but OS and LS evaluated separately.^{5,24,25} The incidence of symptomatic SPVT in these studies was 2.6% with a range of 0.35% to 13% (Table 2). Overall, the incidence of symptomatic SVPT in prospective and retrospective studies with open and laparoscopic splenectomy was 3.3% (85/2590).

Incidence of symptomatic splenic/portal vein thrombosis according to the indication for splenectomy

Table 3 shows the incidence of symptomatic SPVT in various studies subdivided according to the indication for splenectomy in patients with OS or LS. The data were taken from prospective and retrospective studies with mixed populations and from studies in which patients with specific underlying diseases were evaluated. These data show that patients with myeloproliferative disorders, lymphoproliferative disorders and hemolysis (in particular hereditary spherocytosis and thalassemia intermedia) have the highest risk of SPVT, whereas the risk seems to be very small in the case of autoimmune thrombocytopenia (AITP) and after traumatic splenectomy. It should be mentioned that severe SPVT also occurred in some children with hereditary spherocytosis.²⁶⁻²⁸ The highest risk of thrombosis including SPVT has been reported in patients with hereditary stomatocytosis.²⁹

Table 2. Incidence of splenic/portal vein thrombosis after splenectomy in retrospective studies (all adults).

Type of splenectomy	Patients (n)	Symptomatic	Ref.
Laparoscopic	37	2/37, (5.4%)	[5]
Laparoscopic	275	1/275 (0.35%)	[22]
Laparoscopic	68	3/68, (4.4%)	[23]
Laparoscopic	72	4/72, (5.6%)	[24]
Laparoscopic	39	1/39, (2.6%)	[25]
Laparoscopic all patients	491	11/491 (2.2%)	
Open	64	6/64, (9%)	[5]
Open	688	6/688, (0.9%)	[19]
Open	123	10/123, (8.1%)	[20]
Open	563	9/563, (2%)	[21]
Open	86	8/86, (9.3%)	[24]
Open	30	4/30, (13%)	[25]
Open all patients	1554	43/1554, (2.8%)	
Laparoscopic + open all patients	2045	54/2045 (2.6%)	

Risk for postoperative splenic/portal vein thrombosis according to the type of operation (OS or LS)

There is no well-designed randomized trial comparing the risk for SPVT after OS and LS. Tables 1 and 2 show the incidence of asymptomatic and symptomatic SPVT in prospective and retrospective studies in patients with OS and LS. There is obviously no difference in the incidence of SPVT after OS and after LS. These data are not derived from direct comparisons and therefore have to be interpreted with caution. The proportion of high-risk patients (big spleens and hemolysis) and low-risk patients (AITP) was similar in both populations.

Time from surgery to asymptomatic or symptomatic splenic/portal vein thrombosis

The median time from splenectomy to asymptomatic SPVT was six days (range 3-11 days) in a study with contrast-enhanced CT.¹⁷ The median interval between splenectomy and symptomatic SPVT in three retrospective studies was 10.7 (range 4-27) days,²⁴ 11.6 days (range 2-22) 5 and 12 days (range 6-99),²¹ while it was eight days (range 2->28) in published reports on single or small series of cases in which data on the interval between splenectomy and SPVT were provided (Figure 1). Considering all data, we infer that the latency period from the onset of thrombosis to clinical symptoms is on average one week or more.

Incidence of deep venous thrombosis and/or pulmonary embolism after splenectomy

We were not able to identify one single study that specifically evaluated the incidence of asymptomatic or symptomatic DVT/PE in a prospective manner. Symptomatic DVT/PE sometimes occurred concurrently with SPVT.³⁰ In studies with evaluation of symptomatic DVT/PE, the incidence was 1.6% (7/433).^{9,13,25,31} It is uncertain whether in studies in which DVT/PE was not mentioned^{11,12,21,24} the incidence was zero or if the incidence was not specifically evaluated. To date, it is impossible, from the available data, to draw any specific conclusions on the occurrence and prevention of DVT/PE after splenectomy.

Table 3. Incidence of symptomatic splenic/portal vein thrombosis after splenectomy according to the underlying disease (prospective and retrospective studies).

Underlying disease	Total number of patients with SPVT	Ref.
Hereditary hemolytic anemias	11/89, (12.3%)	[5,21,24]
Malignant lymphoma	9/70, (12.8%)	[5,11,17,24]
Myeloproliferative disorders	40/386, (10.3%)	[5,11, 21,24,31,44]
Autoimmune-thrombocytopenia (AITP)	2/118, (1.7%)	[5, 13, 17, 24]
Trauma	0/122	[21]

Antithrombotic prophylaxis

The prophylactic antithrombotic strategies in the various cohorts or cases were extremely heterogeneous and ranged from no systemic prophylaxis,^{6,32} only pneumatic compression^{8,31} to subcutaneous standard or low molecular weight heparin (LMWH).^{9,12,21,24} The duration of heparin prophylaxis ranged from three to more than seven days after surgery. In only a few studies^{9,11,24,25,30} was heparin treatment extended beyond seven days in some of the patients.

Response to treatment and late complications

Most patients with documented SPVT were treated with intravenous heparin followed by oral anticoagulant therapy for a variable time period, in most cases for 3-6 months. In the majority of cases in whom a follow-up investigation was performed ($n=90$)^{5,9,11,12,15-17,20-21,23-25,28,33} there was a documented complete (57/90, 63.3%) or at least partial resolution (13.3 %) of the thrombus. However, in 7.7% the thrombus persisted and in 15.5% cavernoma or portal hypertension were documented. Unfortunately, no long-term studies were performed in these patients. In single cases of hereditary spherocytosis, bleeding from varices due to portal thrombosis occurred decades after splenectomy.^{34,35}

Discussion

Postoperative venous thromboembolism is a serious problem. The incidence of asymptomatic and symptomatic DVT/PE after surgery and its prevention have been evaluated in numerous clinical trials. Surprisingly, none of the studies specifically investigated thromboembolic events after splenectomy and there are no specific recommendations for prevention and management. This is difficult to understand, since splenectomy is not a rare surgical procedure. It is estimated that annually in the USA 35,000,³⁶ in France 5,000³⁷ and in Germany 15,000³⁸ splenectomies are performed.

Our analysis specifically concentrated on the risk of postoperative SPVT. Prospective studies indicate that about 12% of patients have an asymptomatic or symptomatic SPVT following splenectomy. The incidence of symptomatic SPVT ranged from 0.35%-19% in analyzed prospective and retrospective studies. These large discrepancies may be due to differences in the patient populations, methodological variations and varying degrees of clinical awareness of this complication. In contrast to DVT of the leg, where the evaluation of postoperative thrombosis has become highly standardized, this is not the case with SPVT. In all but one study,⁸ color Doppler imaging was the screening method of choice, but it is now well known that contrast-enhanced CT is more sensitive.³⁹ In fact, the incidence of SPVT was at least twice as high when contrast-enhanced CT was used for screening or diagnosis.^{8,17} Another explanation for the above-mentioned discrepancies may be the time points of screening, which were quite variable.^{9,11-13,15}

The definition of risk factors is important for the choice of intensity and duration of postoperative

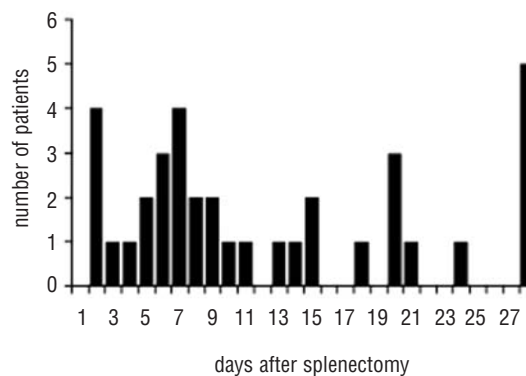


Figure 1. Time points of symptomatic SPVT after splenectomy (case reports). Data from: 9, 11, 20,23, 25-28, 30, 32, 45,46.

antithrombotic prophylaxis. Generally, three groups of risk factors have to be considered: (i) preoperative general clinical or laboratory risk factors, such as age, obesity, previous thrombosis; (ii) the underlying disease (in particular malignant disease); and (iii) factors related to the surgical intervention itself (duration, open or laparoscopic surgery). All these factors are also risk factors for SPVT, but in the case of splenectomy the type of the underlying disease seems to be by far the highest risk factor. Patients with big spleens (mostly patients with myelofibrosis or lymphoma) and patients with hemolysis, in particular hereditary hemolytic anemias (hereditary spherocytosis and thalassemia intermedia) have the highest risk for SPVT.

The introduction of laparoscopic surgery was a milestone in abdominal surgery, in particular for splenectomy.²² Since after laparoscopic surgery patients recover more rapidly and can be discharged from hospital earlier, it has been argued that postoperative antithrombotic prophylaxis may not be necessary, in particular after laparoscopic cholecystectomy.⁴⁰ Only 37% of surgeons in Sweden⁴¹ use thromboprophylaxis in all patients after splenectomy. A randomized study comparing different durations of postoperative thrombosis prophylaxis after laparoscopic abdominal surgery was terminated early because of the low incidence of thrombosis,⁴² but only one patient with splenectomy was included in this study. It has been stated that the same rules for postoperative thrombosis prophylaxis should be applied for open and laparoscopic splenectomy (OS and LS).⁴³ However, all these studies concentrated on the risk of postoperative DVT/PE and did not consider the risk of SPVT. Following splenectomy, the risk of symptomatic SPVT may be higher than that of DVT/PE.^{9,13,25,31} From the results of our analysis it appears that there is no difference in the risk for postoperative SPVT after OS or LS. The main reasons for this finding may be that the mean operating time for LS is longer than that for OS, the damage to the splenic vein may be greater in LS and the pneumoperitoneum may induce venous stasis. The early recovery and shorter hospital stay after LS may reduce the risk for DVT and PE, but is unlikely to influence the risk for SPVT. Thus, adult patients with either OS or LS should be regarded as high-risk patients with

regard to postoperative SPVT and/or DVT/PE. Since the median interval from surgery to asymptomatic SPVT is about six days and to symptomatic SPVT 8-12 days, it seems reasonable to extend the prophylaxis beyond the hospital stay, at least to 2-4 weeks after surgery. A shorter antithrombotic pharmacological prophylaxis may be considered in children and younger adults with AITP and trauma, who have a relatively low risk of thrombosis, but in congenital hemolytic disorders, cases of SPVT have been described even in children.²⁶⁻²⁸ Several cases of SPVT have been described in patients despite prophylaxis with standard or LMWH, but these patients had received prophylaxis for only one week.²¹

Patients with documented asymptomatic or symptomatic SPVT usually received intravenous standard heparin or therapeutic doses of LMWH followed by oral anticoagulant therapy for 3-6 months. More than 90% of asymptomatic⁸ and about 2/3 of symptomatic SPVT resolved completely. SPVT shares this characteristic with pulmonary embolism, where resolution of the emboli within a few weeks is common. In view of these favorable data, aggressive treatment, such as thrombolytic or surgical therapy does not seem to be justified. The long-term outcome of SPVT after splenectomy has not been studied.

We are aware of the limitations of this analysis. The studies we have analyzed were heterogeneous with regard to patient populations, the methods and time points of screening as well as the diagnostic criteria for

symptomatic SPVT. Moreover, the prospective studies were often only small in size and in retrospective studies diagnostic criteria were usually not specified. Nevertheless, our data may be helpful for clinicians involved in the care of splenectomized patients and may also be useful as a basis for the design of future trials. Again, more prospective, large randomized studies are needed to assess the postoperative risk for thromboembolic events after splenectomy.

Authorship and Disclosures

M-TK: substantial contributions to conception and design, acquisition of data, analysis and interpretation of data; drafting the article; final approval of the version to be published. KL: substantial contributions to conception and design, analysis and interpretation of data; revising the article critically for important intellectual content; final approval of the version to be published. EAM N: substantial contributions to analysis and interpretation of data; revising the article critically for important intellectual content; final approval of the version to be published. IP: substantial contributions to conception and design, analysis and interpretation of data; revising the article critically for important intellectual content; final approval of the version to be published.

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