Randomized controlled trial to investigate the impact of anticoagulation on the incidence of splenic or portal vein thrombosis after laparoscopic splenectomy

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Background: Splenic and portal vein thrombosis (SPVT) is a potentially life-threatening complication of splenectomy. There is a paucity of studies examining the role of prophylactic pre- and postoperative anticoagulation in the prevention of this complication. We designed a prospective randomized controlled trial (RCT) to more rigorously address the impact of prophylactic anticoagulation on the incidence of asymptomatic or symptomatic SPVT, detected on Doppler ultrasound, after laparoscopic splenectomy.

Methods: This 2-centre, phase II, prospective, open-label, parallel-assignment RCT compared no postoperative anticoagulation to a regimen of 40 mg of enoxaparin subcutaneously once daily for 21 days. All patients underwent Doppler ultrasonography of the splenoportal system preoperatively and again 14–28 days after surgery to screen for nonocclusive or occlusive thrombosis.

Results: From November 2006 to November 2008, 35 patients were enrolled in the RCT. Four patients withdrew, 1 required conversion to an open procedure and 1 died at 3 months (the cause of death was not related to the study). Of the 29 patients remaining, 15 were randomly assigned to the anticoagulation group and 14 to the nonanticoagulation group. One (3.4%) patient in the treatment group experienced portal thrombosis. Rates of postoperative bleeding were similar in both groups.

Conclusion: This RCT of anticoagulation found a low overall risk of SPVT after laparoscopic splenectomy; however, this is an underpowered study, and further multi-centred clinical trials are needed.

Contexte : La thrombose de la veine splénique et porte (TVSP) est une complication de la splénectomie qui peut menacer la vie. Peu d'études se sont penchées sur le rôle de l'anticoagulation pré-opératoire et postopératoire prophylactique dans la prévention de cette complication. Nous avons conçu un essai contrôlé randomisé (ECR) prospectif afin d'analyser plus rigoureusement l'effet de l'anticoagulation prophylactique sur l'incidence de la TVSP asymptomatique ou symptomatique, détectée par échographie Doppler, après une splénectomie par laparoscopie.

Méthodes : Au cours de cet ECR multicentrique de phase 2, prospectif, ouvert et à répartition en groupes parallèles, nous avons comparé l'absence d'anticoagulation postopératoire à un régime de 40 mg d'énoxaparine administrée par voie sous-cutanée 1 fois par jour pendant 21 jours. Tous les patients ont subi une échographie Doppler du système splénoporte avant l'intervention et de nouveau de 14 à 28 jours après l'intervention afin de dépister la présence d'une thrombose non occlusive ou occlusive.

Résultats : De novembre 2006 à novembre 2008, 35 patients ont été inscrits à l'ECR. Quatre patients s'en sont retirés, il a fallu dans 1 cas procéder à une intervention ouverte et 1 patient est décédé à 3 mois (la cause du décès étant sans rapport avec l'étude). Sur les 29 patients restants, 15 ont été affectés par randomisation au groupe de ceux qui ont reçu une anticoagulation et 14, au groupe des patients qui n'en ont pas reçu. Un patient (3,4 %) du groupe traité a subi une thrombose de la veine porte. Les taux de saignement postopératoire étaient semblables dans les 2 cas.

Conclusion : Cet ECR sur l'anticoagulation a révélé un faible risque global de TVSP après une splénectomie par laparoscopie, mais il s'agit d'une étude qui manque de puissance et d'autres essais randomisés multicentriques s'imposent.

Splenic and portal vein thrombosis (SPVT) is an alarming and potentially life-threatening complication of splenectomy. Prospective and retrospective studies have shown the incidence of symptomatic SPVT to be between 0%¹ and 19%.² Since patients with SPVT can present with vague and nonspecific symptoms, identification of this condition is essential to allow for early treatment and to prevent complications, such as bowel infarction or portal hypertension if the occlusive splenic venous clot propagates beyond the splenoportal confluence. Several studies have looked at using contrast-enhanced computed tomography or Doppler ultrasonography for more sensitive early detection of asymptomatic SPVT in routine surveillance imaging postsplenectomy. The reported incidence of asymptomatic SPVT ranges from 5%³ to 52%,⁴ and the risk very clearly correlates with the degree of splenomegaly, with massive splenomegaly carrying the greatest risk. Patients with myeloproliferative and lymphoproliferative disorders and hereditary hemolytic anemia are also at increased risk for SPVT.⁵ There are currently no well-designed studies to compare the rate of SPVT in open splenectomy versus laparoscopic splenectomy; however, there is a trend suggesting a higher overall incidence of SPVT in the laparoscopic cohort (5%–19% open v. 10%–52% laparoscopic).⁵ Moreover, the administration of routine perioperative anticoagulation is not standardized. The 2008 clinical practice guidelines of the European Association for Endoscopic Surgery (EAES) recommend perioperative anticoagulant prophylaxis with subcutaneous heparin for all patients.⁶ Recent surgical guidelines indicate that routine use of thromboprophylaxis is not recommended for laparoscopic procedures. For patients at increased risk for thrombosis, one or more of the following is recommended: low molecular weight heparin (LMWH), low-dose unfractionated heparin (LDUH), fondaparinux, intermittent pneumatic compression (IPC) or graduated compression stockings (GCS).⁷

Despite a body of literature on the incidence, diagnosis and treatment of SPVT, to our knowledge there have not been any studies examining whether prophylactic pre- and postoperative anticoagulation can prevent this serious complication. We therefore designed a prospective, randomized controlled trial (RCT) to address the impact of more aggressive prophylactic anticoagulation on the incidence of asymptomatic or symptomatic SPVT, detected on Doppler ultrasound, after laparoscopic splenectomy.

METHODS

This 2-centre, phase II, prospective, open-label, parallel assignment RCT addresses the impact of prophylactic anticoagulation in reducing the incidence of SPVT after laparoscopic splenectomy. The study was approved by the Health Research Ethics Board of the University of Alberta (protocol 5698) and by Health Canada, and it was prereg-

istered with ClinicalTrials.gov (NCT00769873). Surgeons in 2 different hospitals in Edmonton, Alta., performing laparoscopic splenectomies recruited patients from their clinical practices. Eligible participants gave consent preoperatively using a standardized and approved research consent form. They were then randomly assigned to the anticoagulation treatment or control groups using a random number table and sealed envelope containing postoperative instructions. The treatment allocations were not revealed until immediately after completion of the surgery. All participants were fitted with pneumatic stockings and received 40 mg of the LMWH enoxaparin (Lovenox; Sanofi-Aventis Canada) subcutaneously 2 hours before surgery, as per standard preoperative orders for both arms of the study. Postoperatively, those assigned to the treatment group received 40 mg of enoxaparin subcutaneously once a day for 21 days; those in the control group received no postoperative anticoagulation. Patients with severe renal impairment received an adjusted dose of enoxaparin (a 30-mg subcutaneous dose daily). Prior to discharge from hospital, all participants in the treatment arm were instructed by a registered nurse on the proper technique of subcutaneous injection and either self-administered therapy or received therapy from a home-care nurse when appropriate. All patients underwent baseline Doppler ultrasonography of the splenic and portal system preoperatively and again 14–28 days postsurgery to monitor for the presence of nonocclusive or occlusive SPVT. The patients also underwent routine blood work to monitor for bleeding and serial platelet counts to screen for heparin-induced thrombocytopenia and clinical response to splenectomy.

All surgeries were initiated laparoscopically, and intraoperative decision-making was used to decide when hand-assisted laparoscopic splenectomy (HALS) for the removal of larger spleens was indicated. Patients treated with HALS were included in the study, whereas those who required conversion to open surgery were excluded from the trial. All surgeons, anesthesiologists and assistants were blinded to the random assignment of the patient until completion of the surgery to minimize potential bias in surgical technique. Radiologists who performed follow-up abdominal ultrasonography and interpreted the results were also blinded to the participants' random assignment. We checked compliance with subcutaneous injections by follow-up phone calls to patients who could be reached by telephone.

Statistical analysis

To fully define the overall potency of the anticoagulation regimen and to achieve 80% power to detect a reduction in the incidence of SPVT from 22.5%⁸ (control group) to 10% (treatment group), the study would require about 214 participants (107 per arm). We used Student *t* tests

and Fisher exact tests to compare the baseline characteristics between the 2 groups.

RESULTS

From November 2006 to November 2008, 35 participants were enrolled in this 2-site RCT. Four participants withdrew from the study and 2 were excluded: 1 patient required conversion to an open approach (owing to the large size of the spleen), and 1 patient died 3 months post-surgery from myocardial infarction that was unrelated to the procedure or study medication. This patient could not be included in the thrombosis analysis because he did not undergo postoperative ultrasonography before his death. Of the remaining 29 participants, 15 were randomly assigned to the anticoagulation group and 14 to the non-anticoagulation group. Patient characteristics are summarized in Table 1. There were no statistically significant differences between the 2 groups.

Of all 29 patients who completed the study, only 1 case (3.4%) of SPVT was detected on the postoperative Doppler ultrasound. This patient was in the treatment group and was compliant with the subcutaneous injections. The risk difference between the anticoagulation group and the nonanticoagulation group was 0.067 (95% confidence interval [CI] -0.596 to 0.193), which was not statistically significant ($p = 1.00$). The indication for surgery for the patient with SPVT was massive splenomegaly, and comorbidities included chronic hepatitis B and a history of malaria. Medications included the birth control pill (Alesse 21). The patient's preoperative ultrasound showed a spleen size of $12 \times 19 \times 7$ cm, and the weight determined post-

operatively from the complete pathology sample was 986 g. The patient was completely asymptomatic when her routine postoperative ultrasound showed complete occlusive thrombosis of the splenic vein with partial, nonocclusive portal vein thrombosis. She was readmitted to hospital for several days and was treated initially with subcutaneous enoxaparin and subsequently with therapeutic oral warfarin for a total of 6 months. Doppler ultrasonography was repeated 6 months postoperatively and demonstrated complete resolution of the SPVT. Postoperative blood work showed an increasing trend in her platelet count, with a peak of $1141 \times 10^9/L$ on the day of her diagnosis of SPVT. Her white blood cell count remained stable postoperatively.

Two patients, 1 in each group, experienced bleeding complications requiring reoperation and transfusion. Both patients were appropriately resuscitated, anticoagulation was withheld temporarily in the patient in the treatment group, and there were no long-term consequences (Table 2).

DISCUSSION

To our knowledge, this study represents the first and only prospective RCT for the investigation of SPVT after laparoscopic splenectomy. The incidence of asymptomatic SPVT has been reported to be 10%–52% for laparoscopic splenectomy. In the current study, using Doppler ultrasonography, the overall incidence of SPVT was 3.4% (1 of 29 patients). The relatively low proportion of participants with myeloproliferative disease, lymphoproliferative disorders and hereditary hemolytic anemia may have contributed to our relatively low incidence of SPVT.⁵

Table 1. Demographic and clinical characteristics of patients enrolled in a randomized controlled trial investigating the impact of anticoagulation therapy on the incidence of splenic or portal vein thrombosis

Characteristic	Enoxaparin	No enoxaparin	<i>p</i> value
Total no. of patients	15	14	
Age, yr			0.28
Median (range)	59 (17–72)	46 (18–74)	
Mean (95% CI)	51 (41–61)	43 (31–55)	
Sex, male:female	11:4	5:9	
History of thrombotic events or malignancies	2	0	0.48
Type of disease, no.			
Immune thrombocytopenic purpura	5	10	0.07
Thrombotic thrombocytopenic purpura	1	2	0.60
Chronic lymphocytic leukemia	2	1	1.00
Lymphoma	2	1	1.00
Hereditary spherocytosis	1	0	1.00
Other	4	0	0.10
Duration of surgery, mean (95% CI) min	95.3 (77.7–113.1)	92.8 (78.8–106.8)	0.80
Spleen weight, mean (95% CI) [range] g	627.5 (334.3–920.7) [60–1670]	294.3 (96.9–491.6) [77–1300]	0.06
Postoperative day 1 platelet count, mean (95% CI) $\times 10^9/L$	172 (120–224)	196 (87–304)	0.66
Length of stay in hospital, mean (95% CI) d	3.07 (2.10–4.04)	2.86 (1.77–3.95)	0.76
CI = confidence interval.			

Contrary to expectation, the single incidence of SPVT in our study occurred in the enoxaparin treatment anticoagulation group. However, this patient may have had additional contributing factors to her thrombosis, potentially her oral contraceptive use or chronic hepatitis B causing inflammation. Proteins C and S, antithrombin III and factor V Leiden were not measurable on thrombophilia screens while the patient received anticoagulation, and results were not available subsequently. Alternatively, her postoperative thrombocytosis may have contributed to the development of SPVT. Whereas the overall incidence of SPVT detectable on Doppler ultrasound was low in the current study, the addition of 40 mg of enoxaparin daily for 3 weeks postoperatively failed to prevent this complication in our patient.

The literature suggests that the median interval for the development of asymptomatic SPVT is at least 6 days, and that for symptomatic SPVT is at least 8–12 days, providing rationale for extended anticoagulation for up to 3 weeks after surgery.⁵ The ENOXACAN II study provides evidence that prolonged anticoagulation is safe and more effective in reducing the incidence of venographically demonstrated thrombosis compared with standard 1-week anticoagulation prophylaxis.⁹ Very few studies of SPVT extend the prophylactic anticoagulation regimen beyond 7 days, which makes our study unique. In designing this trial, LMWH was chosen over LDUH, as Peitribissa and colleagues⁸ reported a 22.5% incidence of splenic vein thrombosis progressing to portal vein thrombosis in 12.5% of their patients despite prophylactic anticoagulation with subcutaneous LDUH for 7 days postoperatively. In a recent prospective study of 146 patients (mixture of laparoscopic and open splenectomy), the incidence of portal system thrombosis was 4.8% (7 of 146 patients) despite the use of LMWH when indicated for mild to severe risk of deep venous thrombosis. This is comparable to our reported incidence of 3.4%. Recent reports question whether the technique used for splenic vessel ligation (stapled vascular transection en masse) may contribute to the increased rate of thrombosis in patients who undergo laparoscopic versus open techniques.¹⁰ Our centre consistently uses a laparoscopic vascular stapler for control of the splenic hilum, and owing to the low incidence of SPVT observed, we do not believe that this surgical technique contributed to our 1 case of SPVT. Our reported bleeding complication rate was 7%, as compared with the 4%

reported by the Lovenox monograph;¹¹ however, owing to our small sample size, we cannot draw any meaningful conclusions. Our results compare favourably with that of a study showing a reoperation rate of 5% (2 of 40 patients).⁸

Limitations

The major drawback of the current study is that it was substantially underpowered to detect significant differences between the groups and was limited by patient accrual rates within our city. After 2 years of active recruitment within our centres, we were only able to enrol 35 patients. We attempted to extend the study as a multi-centre initiative across Canada and selected sites in the United States but have thus far lacked funding support for an adequately powered study.

Based on the current limited findings, we cannot draw any significant and meaningful conclusions about the use of a prophylactic dose of 40 mg of subcutaneous enoxaparin once daily in the prevention of SPVT after laparoscopic splenectomy, but this study provides safety and feasibility data and is a good exploratory trial to power a definitive trial based on the long-term anticoagulation strategy. A multicentre trial is needed to achieve the numbers needed for an adequately powered study.

CONCLUSION

To our knowledge, this study represents the first such attempt to rigorously investigate the impact of perioperative prophylactic anticoagulation after laparoscopic splenectomy in the form of an RCT. The overall rate of thrombosis was low (3.4%). Treatment with 40 mg of enoxaparin once daily failed to prevent the single case of SPVT in the treatment group, suggesting that enoxaparin once daily may be insufficient to prevent SPVT. However, the sample size needed for an adequately powered study was not met owing to low enrolment. A further multi-centre RCT is clearly needed to more definitively answer this question.

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Competing interests: None declared.

Contributors: Drs. Wang, Brisebois, Sample and Shapiro designed the study. Drs. Wang and Kopac acquired the data, which Drs. Wang, Kopac and Shapiro analyzed. Drs. Wang, Kopac and Shapiro wrote the article. All authors reviewed the article and approved its publication.

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Table 2. Study outcomes in the anticoagulation versus the nonanticoagulation groups

Outcome	Group; no.	
	Anticoagulation	Nonanticoagulation
Total	15	14
Thrombosis	1	0
Bleeding	1	1

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