original research report

Systemic thromboembolic complications after laparoscopic splenectomy for idiopathic thrombocytopenic purpura in comparison to open surgery in the absence of anticoagulant prophylaxis

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BACKGROUND: Idiopathic thrombocytopenic purpura (ITP) in adults has a chronic course and may necessitate splenectomy. The current study was undertaken to study the systemic thromboembolic complications of laparoscopic splenectomy (LS) versus open splenectomy (OS) in patients with ITP at two large referral hospitals.

PATIENTS AND METHODS: We conducted a retrospective analysis of 49 patients who underwent splenectomy (21 LS and 28 OS) for primary/relapsing refractory ITP between June 1995 and November 2004. Clinically and/or radiologically confirmed deep venous thrombosis (DVT) and/or pulmonary embolism (PE) were assessed within 2 weeks before and after splenectomy. None had prophylactic anticoagulants immediately after surgery. Follow up of those who developed complications continued for at least 2 additional years to assess for contributing factors that may have been masked at the time of occurrence.

RESULTS : Two (9.5%) LS group had acute PE within 5 days of LS and their platelet count reached 500×10^3/μL within 4 days and 1000×10^3/μL within 7 days after surgery. Three conversions to OS occurred; none had VTE. DVT occurred in 3 patients (10.7%) in the OS group; none were life threatening. There were no deaths.

CONCLUSION: Life-threatening venous thromboembolic events are serious complications after LS and OS for ITP patients if prophylactic anticoagulants are not administered. Patients at risk are those who both have an exponential rise of the platelet count, although factors other than the platelet count may be contributing in OS. Postsplenectomy, ITP should be considered as a thrombophilic condition and studies of additional measures to prevent such events are warranted.

Idiopathic thrombocytopenic purpura (ITP) is an autoimmune disease characterized by development of autoantibodies that bind platelet membrane glycolproteins and active complement activation, leading to rapid clearance of the platelet-antibody complex via the hemophagocytic system mainly in the spleen. In adults, initial treatment with steroids and/or intravenous immunoglobulins can induce a response. However, upon withdrawal or tapering of steroids the majority relapse.[1]

Splenectomy represents a strategic curative procedure for the majority of patients with chronic ITP who fail to respond or relapse after primary medical treatment.[2] Although laparoscopic splenectomy (LS) has been introduced relatively recently (in 1990s), its application has witnessed a larger scale use at many centers due to its advantage of being "endoscopic', less traumatic, and less disfiguring with a relatively short stay; it is also supposed to be associated with fewer complications,[3-5] including life threatening events and peri-operative mortality.[6] Its application is ideal when the splenic size is small or nonpathologic as in cases of ITP. When splenectomy is done via an open approach and in clonal disorders, precautions for deep vein thrombosis (DVT) prophylaxis are usually applied due to the heightened

risk of venous thromboembolism (VTE) that is associated with the underlying disease. However, due to the bleeding tendency with ITP and the relatively short duration of the procedure when the laparoscopic approach is taken, no prophylactic anticoagulants are usually administered.[7,8] Due to an absence of prospective studies discussing the need for thromboprophylaxis in such a situation in this target population of patients, universal guidelines for VTE prophylaxis in ITP are lacking although they are sorely needed.[9]

Thromboembolic complications, including DVT, pulmonary embolism, portal vein thrombosis, inferior vena caval thrombosis and mesenteric vein thrombosis may occur in an average of 10% of patients with hematological diseases undergoing splenectomy. However, the incidence may range between 1% to 75%, depending on the underlying hematological disease and the clinical situation as well as the occurrence of postoperative complications like infections and prolonged recumbency.[8,10]

The advantages of the laparoscopic approach in ITP patients that have been reported are shorter operation time, decreased estimated blood loss, decreased length of hospital stay and less chance of conversion to open splenectomy (OS) than in any patients with any other diagnosis.[11] Therefore, LS has become the procedure of choice for patients with medically refractory ITP requiring removal of the spleen. Surgeons who are seeking to undertake, or who currently are practicing this procedure, should be aware that it is considered an advanced laparoscopic procedure and is associated with a significant learning curve that has yet to be defined.[12] Much of the pertinent data published in the surgical journals are focused mainly on the effectiveness in curing ITP, hospital stay, cost effectiveness or postoperative infectious complications or bleeding and/or thrombosis.[13-15] Few studies have comprehensively reported systemic thromboembolic complications, like DVT and or pulmonary embolism without detailed mention of factors contributing to such events or suggestions for preventive measures.[13] However, most of the available studies suffer from a small sample size (less than 20 patients), lack long-term follow up and sometimes include other hematological disorders with unclear thromboprophylaxis strategy.[5] The current study was undertaken to study the systemic thromboembolic complications of LS in comparison to OS done for patients with ITP who did not received anticoagulant thromboprophylaxis at Ain Shams University Hospitals, Cairo, Egypt and North West Armed Forces Hospitals, Saudi Arabia with a minimum follow up of 2 years (range 2-4 years).

PATIENTS AND METHODS

The study was a retrospective analysis of 49 consecutive patients with a preoperative diagnosis of ITP who underwent splenectomy (21 laparoscopic and 28 open) by two separate teams at Ain Shams University Hospital, Cairo, Egypt and North West Armed Forces Hospital, Tabuk, Saudi Arabia, from June 1995 to November 2004. Those who developed systemic VTE were further followed for at least 2 years post-splenectomy. The majority of patients had been referred from teaching hospitals and private clinics. Splenic or portal vein thrombosis was not systematically or prospectively sought in our study.

All patients fulfilled the ITP definition proposed in guidelines,[16] namely: (1) the presence of thrombocytopenia before treatment; (2) either a normal or increased number of megakaryocytes in the bone marrow; (3) no history of recent ingestion of a drug known to induce thrombocytopenia; (4) no congestive splenomegaly; (5) no known history of secondary immune thrombocytopenia, sepsis, or intravascular consumption. Initial work up of patients before starting steroids and before splenectomy followed the American Society of Hematology Guidelines.[17] Special attention was made to the normal/or increased number of megakaryocytes with defective budding and to the absence of any other intrinsic bone marrow abnormalities. Review of bone marrow biopsies and peripheral smears was undertaken before splenectomy.

The indications for splenectomy were primary refractory ITP or relapsing refractory ITP that failed the first-line therapy (steroids/intravenous immunoglobulin [IVIG]) or needed unacceptably high doses of steroids to maintain a safe platelet count and prevent bleeding, failed high-dose steroids for 2 weeks with a platelet count of $10\times10^3/\mu L$ or less. Also included were patients who were bleeding with a fluctuating platelet count above $10\times10^3/\mu L$ but below $30\times10^3/\mu L$. Primary treatment was steroids at 1 mg/kg/day unless otherwise specified. None received monoclonal antibody therapy (rituximab). Platelet transfusion was allowed immediately before or during the procedure in patients with a platelet count $<30\times10^3/\mu L$ for laparoscopic and $<10\times10^3/\mu L$ for open splenectomy in the absence of bleeding. For those who were taking prednisone before surgery, a switch to hydrocortisone during surgery at the dose of 50 mg IV every 6-8 hours was usually practiced until the patient was able to tolerate oral intake. Of the 28 OS patients, 26 had elective open splenectomy; two patients an underwent emergency procedure due to failure of steroid therapy and IVIG primary treatment and multiple salvage lines of therapy

(vincristine, high-dose pulse steroids, danazol, repeated IVIG) with a bleeding tendency. The laparoscopic splenectomy was performed as described elsewhere[18] with the patient in a left semi-decubitus position under general anesthesia. Open splenectomy was done according to the international standard through a left subcostal or midline incision. For post-splenectomy response, outcome was assessed according to the criteria proposed by George et al.[19]

Diagnosis of VTE depended on clinical as well as radiological assessment with spiral CT of the chest (pulmonary embolism [PE] study), echocardiogram, electrocardiogram, and Doppler US of the lower limbs on the abdominopelvic veins. In those with PE, Doppler US of the hepatosplenic bed and inferior vena cava were also done. D-dimers level was introduced lately (2004) as part of VTE work up, but was not essential.

Statistical analysis was carried out using the StatView 4.5 and Prism 3.0 software. A two-tailed *P* value equal to or less than .05 was considered statistically significant (*t* test). Kaplan-Meier curves were used to estimate the cumulative rate of VTE in the first 30 days postsplenectomy. The average duration of stay postsplenectomy was calculated from the time of anesthesia until the time of discharge.

RESULTS

A total of 49 consecutive adult patients (14 males, 35 females) with ITP underwent splenectomy (21 laparoscopic and 28 open) by the same teams and at the same units in 2 hospitals between 1995 and 2004 (Table 1). None received prophylactic anticoagulants or antiplatelet agents. There were no deaths in either group. No cases of accessory spleens were detected intraoperatively or with follow up of relapsed cases. The median (range) age of the LS group (31 [18.9] years) was younger than the OS group (38 [17.7] years) with nearly the same duration of disease. The LS group had a higher mean platelet count ($48\times10^3/\mu L$) before the procedure compared to the OS group ($18\times10^3/\mu L$) (*P*=.028).

Two (9.5%) of the 21 LS patients had clinically manifested acute PE (one also had iliofemoral thrombosis); both occurred within the first week of splenectomy. The platelet count of the two patients reached a million within 7 days and 500 $\times10^3/\mu L$ within 4 days after surgery. Three conversions to OS occurred; none had VTE. Postoperative recovery time was not prolonged in the VTE patients and no immobilization was reported. None of the VTE patients had any infections. In OS group, DVT occurred in one patient at a platelet count of $380\times10^3/\mu L$ on the fifth postoperative day, one at a platelet count of $120\times10^3/\mu L$ on the eleventh day, and a third at a platelet count of $150\times10^3/\mu L$ on the thirteenth day . There was no significant difference in estimated blood loss, length-of-stay, or time to oral intake between the two groups. The mean (SD) duration of stay was 4.8 (2.9) days for LS and 3.7 (2.1) days for OS (*P*=.04).

Table 1. Epidemiologic and perioperative features of patients (n=49).

	Laparascopic splenectomy (n=21)	Open splenectomy (n=28)
Median age in years (range)	31 (17-52)	38 (15-58)
Female	17 (81)	18 (64)
Duration of ITP in months (range)	17.5 (6.5-42)	14 (1.5-57)
Primary refractory	3 (14)	6 (21)
Relapsing refractory*	11 (52)	16 (57)
IVIG use before** surgery	6 (29)	4 (14)
Platelet rise to >40 k before surgery[a]	16 (76)	13 (46)
Mean Platelet count on day splenectomy[b] ($\times10^3/\mu L$) (range)	48 (11-227)	18 (<10-314)
Vaccination before splenectomy[c]	16 (62)	11 (39)
Mean hemoglobin (g/dL) (range)	12.3 (9.1-15.7)	13.1 (8.7-16.5)
Intra-operative platelet transfusion	4 (19)	6 (21)
Intra-operative blood transfusion	None	2 (7.1)
Post-operative platelet transfusion	4 (19)	4 (14)
Pos-operative blood transfusion	2 (10)	5 (18)
Postoperative other complications		
Wound infection	1 (5)	2 (7)
Sub-phrenic abscess	1 (5)	1 (4)
Bleeding	2 (10)	2 (7)
Conversion to open surgery	3 (14)	---
Mean operative time (minutes)	175 (140-230)	185 (110-210)
Anticoagulant prophylaxis	None (0)	None (0)

Values are n(%) unless otherwise indicated. [a]*P*= .07, [b]*P*= .037, [c]*P*= .015.

Complications

Two of the 21 (9.5%) patients in the LS group developed clinically manifest acute pulmonary embolism (one also had iliofemoral thrombosis); both occurred within 5 days of LS and their platelet count reached $500\times10^3/\mu L$ within 4 days and a million within 7 days. Moreover, they also had the lowest baseline platelet count ($<10\times10^3/\mu L$) before LS for more than 3 weeks with failure to respond to steroids and IVIG. Three conver-

Table 2. Systemic thromboembolic complications post-splenectomy (n=49).

Feature	Laparoscopic splenectomy (n=21)	Open splenectomy (n=28)
VTE		
Life threatening	2 (9.52)	None
Not life threatening	None	3 (10.7%)
Time to manifest VTE	5 days, 4 days	5, 11, 13 days
Secondary disease	1 case progressed to HES	1 case SLE
Time to manifest underlying secondary disease	6 months (1 patient)	11 months (1 patient)
Presentation Place Onset and clinical presentation	Inpatient (n=1), at home (n=1), sudden SOB (n=2), dizziness for several hours then shock, acute respiratory failure	All with relatively slower rate over a few days, swelling, pain (n=3), and low grade temp (n=1)
Age (y) of VTE cases	34, 29	30, 24 and 42
Sex of VTE cases (F/M)	2/0	2/1
Mortality	None	None

Values are n(*s*) unless otherwise indicated. HES: hypereosinophilic syndrome. SOB: shortness of breath.

sions to OS occurred; none had VTE. One was a single female aged 34 years was found to have PE at a platelet count of $520\times10^3/\mu L$ on the fourth day. However, she reported painful left lower limb swelling the night before. This necessitated extension of admission and systemic anticoagulation. She also bled postoperatively and required 2 units of packed red cell transfusion, but no revision or re-exploration was needed; the patient remained in hospital for 7 days. Within 2 weeks, the platelet count rebounded to $1050\times10^3/\mu L$ and she was treated and maintained on hydroxyurea for 6 months to keep the platelet count within $600\times10^3/\mu L$. After 6 months she developed progressive hypereosinophilia (eosinophils 4500/ μL) with a fluctuation of platelet count between $55\times10^3/\mu L$ to $780\times10^3/\mu L$ followed by a constellation of clinicopathologic findings of primary hypereosinophilic syndrome. Cytogenetic studies of the bone marrow did not disclose an abnormal cytogenetic pattern. Molecular testing for BCR/ABL was negative. The second patient was a 29-year-old female who was also 12 months postpartum and lactating. She had persistent pain after surgery and incompletely opened her bowel before discharge with a marked decrease in her oral fluid intake due to the persistent pain at the site of the laparoscope. She was discharged on the third day 43 hours postsplenectomy. The platelet count was $110\times10^3/\mu L$ on the second day, $270\times10^3/\mu L$ on the third day and $570\times10^3/\mu L$ on the fourth day. No underlying disease was found at the 4-year follow up.

In the OS group, systemic VTE in the form of DVT occurred in 3 patients (11%). None were life threatening. One patient had unilateral iliofemoral DVT within 5 days of OS at a platelet count of $300\times10^3/\mu L$ and two had popliteal DVT at a platelet count of $150\times10^3/\mu L$ and $120\times10^3/\mu L$; the later developed clinical lupus with nephritic syndrome a year later. None of the cases showed a rapid rise of the platelet count more than $300\times10^3/\mu L$ over a week. Both the first and the second patients were also cushingoid with significant obesity (>25% increase in body mass index) and the second one had IVIG presplenectomy in preparation for splenectomy. Due to skin thickness and obesity, they stayed in the hospital longer than other patients. Other complications were wound infection (n=20), subphrenic abscess (n=1) and bleeding (n=3). No accessory spleens were detected.

DISCUSSION

The occurrence of VTE in the immediate (within 1 month) postsplenectomy period (laparoscopic and open) in our study with such a significant incidence (9.5% and 10.7%, respectively) in the absence of anticoagulant prophylaxis indicates clearly that the postsplenectomy period is an acquired "thrombophilic condition" even if the underlying disease for which splenectomy is done is a bleeding one. Clearly any surgery heightens the risk of thrombosis to a wide degree depending on various additional risk factors. It is reported to be higher in the elderly undergoing prolonged splenectomy for malignant hematological conditions and is expected to be much lower with younger age and with the laparoscopic approach in apparently normal and small spleen patients, as in ITP. The proposed mechanisms of thrombosis in such cases include thrombocytosis, leukocytosis, dehydration, subclinical or overt infections, prolonged recumbence, and local injury of the tail of the pancreas or even very prolonged surgery alone.[8] Postsplenectomy thrombocytosis may reach a $1000\times10^3/\mu L$ in some patients and predispose to thrombosis locally at the portal or mesenteric veins or distally and systemically in the form of DVT and/or PE. The association between postsplenectomy thrombocytosis and VTE is unclear, particularly in ITP patients since not all patients with thrombocytosis develop VTE and VTE occurred in some patients without thrombocytosis.[20,21] A relatively recent study investigating the etiology and clinical significance of thrombosis found a higher incidence of venous and arterial thrombosis in patients with primary as compared to secondary thrombocytosis (12.4% vs. 1.6%). The authors conclude that postsplenectomy

thrombocytosis is not associated with an increased risk of thrombosis.[22] However, the clinical features and perioperative prophylaxis were not detailed in the study. Rapidly recovering platelet count in the midst of preoperative status of an up-regulated coagulation cascade and cytoadhesion molecules on both platelet membrane and endothelial cells before surgery with an exponential increase of platelet count with surgery seems a plausible explanation for thrombosis that may occur even in the absence of thrombocytosis.[23] However, there are no data correlating the rapidity of recovery and overshooting of the platelet count and the incidence of thrombosis, especially DVT and PE, probably because the number of patients developing such a complication is still low and the data on LS in such patients is scarce.[12] The additional impact of an increased white cell count has not been studied and is difficult to interpret from the available reports, although it may be operational but it has been described before in relation to the myeloproliferative diseases, mainly polycythemia vera and sickle cell diseases with autosplenectomy.[24] Fontana et al[25] reported increased procoagulant cell-derived microparticles (C-MP) in splenectomized patients. The levels of all the cellular microparticles from red cells, white cells, and endothelial cells increase in ITP patients after splenectomy whether this is laparoscopic or open. Interestingly, increased red cell C-MP was linearly correlated to and associated with shortened activated partial thromboplastin time (APTT) and increased activity of the coagulation factors VIII (P=.023), IX (P=.021) and XI (P=. 009).

Splenectomy itself as a surgery—whatever the approach—represents a thrombogenic stress, but it is not usually associated with high risk for thrombotic complication unless other significant other risk factors are also operational. An extremely low incidence of VTE has been reported by a large French study of 275 laparoscopic splenectomies for patients with various hematological disorders, including ITP (1 %).[7] Only 1 of 12 patients with ITP developed portal vein thrombosis (PVT) without any further systemic thrombosis in an Italian study.[26] Such a small number may be difficult to evaluate particularly in absence of a comparative group. Cordera et al,[5] reported the same very low rate of thrombosis in 1 of 42 laparoscopic and in 2 of 44 open splenectomies without delineating the sites of VTE. Vianelli et al[27] alluded to the relatively better technical and postoperative outcomes—including thromboembolic complications in patients with ITP who underwent LS compared to those with other malignant hematological disorders. However, the rate of systemic VTE was extremely low in ITP patients in their study. Similarly, Zamir et al[28] reported no single VTE event in any of his 17 patients who underwent LS; 15 were ITP. Tanoue et al[29] reported on 41 ITP patients who underwent LS and 64 OS, but did not mention postoperative VTE in either group probably because most of the follow up of these patients had been with their relevant hematology service; therefore many of cases could have been missed. This highlights the paucity of data on paradoxical thrombosis in such a bleeding disorder. Although the total number of patients is small, Lozano-Salazar et al[30] reported PE in 1 of 6 patients who underwent LS while none of the other 10 patients who underwent OS manifested any reportable VTE. No details pertinent to that patient were added. Schlinkert and Mann[31] reported on 21 ITP patients (17 underwent open and 7 laparoscopic splenectomies) and none in the LS group developed VTE, but as mentioned by the authors, this may have been due to patient selection. Svensson et al[32] reported a total of 7 patients who developed thromboembolic complications out of 69 patients who underwent splenectomy (39 LS and 30 OS) for various hematological disorders, including malignant hematological disorders (37 patients), hypersplenism, hemolytic anemia and ITP. The overall incidence of VTE was 7 out of 69 (10%) in spite of the use of short-course prophylactic anticoagulants in those with malignant hematologic disorders. Surprisingly, the only two patients who developed lower limb DVT belonged to the ITP patients who underwent laparoscopic splenectomy, but they did not receive thromboembolic prophylaxis as did those with malignant disorders. The remaining 5 cases of VTE occurred in those with malignant disorders were localized to the portal vein. No clear explanation was discussed by the authors regarding the contributing factors to DVT in the ITP group. Although there is another possibility that silent DVT may be present before surgery, this looks unusual and remote with true isolated ITP patients. Mastrojeni et al[33] indicated that DVT and pulmonary embolism are the dangerous and serious complications in patients who underwent pneumoperitoneum with CO_2 during laparoscopic abdominal surgery. The authors suggested that modern diagnostic tools can make it possible to identify preoperatively relatively silent clinical thrombosis, which can also be detected with laboratory tests (i.e., D-dimer plasma levels) and stressed the importance of a careful preoperative evaluation of the venous system, by Doppler study, to identify patients at risk of DVT and establish a suitable anti-thrombotic prophylaxis. The patient who developed DVT and PE and then hypereosinophilic syndrome (HES) may have possibly been harboring a silent DVT before laparo-

scopic splenectomy due to her underlying pre-clinical HES. Malignant hematological disorders, especially myeloproliferative neoplasias, are associated with a significantly higher rate of thromboembolic complications in the extremities as well as in the visceral veins. Nevertheless, thromboembolic complications may predate the overt appearance of the disease.[34] Further evaluation and stratification of the risk of thrombosis is required as the risk varies with time and with recovery of the platelet count. There is little evidence that the method of splenectomy (open vs. laparoscopic) has an impact on subsequent thromboembolic complications.[8] The effect of splenectomy on accelerating the overt manifestation of an underlying disease (HES in LS and SLE in OS) cannot be completely excluded as in the case with HES who manifested her overt clinical features of the disease a few months after splenectomy with hypereosinophilia, pulmonary involvement and eosinophilic gastritis. Surprisingly, her platelet count fluctuated widely with two episodes of relapses of her thrombocytopenia off steroids with a rebound to over a million on intermediate doses of steroids and normalization of platelets at low intermittent doses (20 mg every other day). The same may also hold true for the SLE patient who presented 11 months later with nephritic syndrome and antiphospholipid antibody syndrome that proved to be lupus in origin, although his platelet count remained within the normal range at the time of presentation with frequent fluctuation and frequent relapses of his autoimmune thrombocytopenia over 2 years at the last follow up. The significant rate of thrombosis and the life-threatening nature of the presentation does not seem to relate to the cumulative experience of the center or the personnel[12] because cases of PE and/or extensive DVT were late comers who had splenectomy after 8 to 9 years of cumulative experience at both institutes. In addition, ITP spleens are relatively normal in size, representing the "ideal" spleens for removal by laparoscopy. Moreover, such serious VTEs do not seem to relate to the technical outcome of the procedure (operative time, intraoperative details, conversion and postoperative pain), but to the systemic acquired thrombophilic status that is heightened after splenectomy and may also be related to the underlying disease of HES that manifested later. Because all patients who developed DVT were relatively young and the splenectomy procedure is a relatively short procedure, other operational factors like hereditary thrombophilic conditions factor V Leiden mutation, prothrombin mutation and coagulation factor inhibitor deficiency (protein C and Protein C and ATIII) should also be sought as it is known that such abnormalities are relatively not uncommon among whites.[35] Hypothetically, laparoscopic splenectomy may have given the patients and the care givers a false sense of safety after the procedure that may explain the life threatening or extensive nature of the VTE at the time of presentation.

In conclusion, ITP patients are not immune from developing PE and or DVT after splenectomy whether open or laparoscopic. Patients at risk are those who have an exponential rise of the platelet count. It may occur even after discharge at home and extra caution should be undertaken for proper prophylaxis and management to avoid such life-threatening situations. We should not differentiate between laparoscopic vs. open splenectomy when formulating anticoagulant indications. Consideration of additional risk factors should be factored into the management plan to optimally prevent the occurrence of such complications. Close monitoring of platelet count should be considered. Nonetheless, early mobilization good hydration and starting prophylactic anticoagulants at an early period of time once hemostasis is systemically and locally secured should be practiced. Prophylaxis with antiplatelet agents such as aspirin needs further study in cases with extreme thrombocytosis (1 million/μL)as it is not expected to be associated with bleeding tendencies as compared to cases of essential thrombocythemia.[36]

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