

Laparoscopic Splenectomy for Primary Immune Thrombocytopenia: Clinical Outcome and Prognostic Factors

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Abstract

Background: Laparoscopic splenectomy (LS) is considered the standard treatment for patients with refractory primary immune thrombocytopenia (ITP).

Patients and Methods: All patients with ITP who underwent LS during the last 17 years and who had a minimum follow-up of 1 year were included. Several perioperative variables such as age, platelet count, and duration of preoperative therapy were recorded and analyzed, looking for potential predictive variables of clinical response.

Results: In total, 150 patients were included: 108 (72%) women and 42 (28%) men, with a mean age of 37.3 ± 15.8 years. In the evaluation 1 year after surgery, 133 (88.7%) patients had achieved complete response, 4 (2.7%) had a response, and in 13 (8.6%) there was no response. None of the analyzed preoperative variables was identified as a predictive factor of response at 1 year. Immediate responders after surgery ($\geq 150,000$ platelets/mL during the first week) had a higher platelet count and rate of complete response at 1 year (94.2%).

Conclusions: LS has a high success rate in patients with refractory ITP. Potential predictive indicators of success remain to be determined.

Background

PRIMARY IMMUNE THROMBOCYTOPENIA (ITP) is an acquired immune-mediated disorder characterized by isolated thrombocytopenia, defined as a peripheral blood platelet count of $< 100 \times 10^9/L$, in the absence of any obvious initiating and/or underlying cause of the thrombocytopenia such as infection, drugs, and autoimmune diseases. The annual incidence of ITP in the United States is approximately 5.5 per 100,000 persons, and the rate increases with age, reaching 12 times higher in populations older than 60 years.¹

Medical treatment of ITP includes corticosteroids, immunosuppressors, androgens, and intravenous immunoglobulin with variable outcomes.² Splenectomy is indicated in patients with refractory or recurrent ITP. With the advent of minimally invasive surgery, laparoscopic splenectomy (LS) was rapidly incorporated for the treatment of these patients.³ Many authors have reported comparable results between the open and laparoscopic approaches of splenectomy.⁴ Moreover, they have observed complete response in up to 90% of the patients after surgery.^{5,6}

Some factors have been associated with different levels of response after splenectomy. Younger age, higher preoperative platelet count, shorter time between diagnosis and surgical treatment, previous response to steroids, and a rapid increase of the platelet count after surgery have been suggested as positive predictive factors of response.⁶⁻¹⁰ By contrast, other studies have failed to confirm the predictive value of these variables.¹¹

Patients and Methods

A cohort of 150 patients with ITP who underwent LS at our institution between January 1995 and March 2012 and had a minimum follow-up of 1 year were included in the study. All patients fulfilled the diagnostic criteria of ITP according to Karpatkin et al.,¹² which include an abnormally low platelet count ($< 100 \times 10^9/L$), in the absence of splenomegaly, with a normal or increased number of megakaryocytes in the bone marrow and no other causes of thrombocytopenia.

Patients were stratified into three groups according to the guidelines of the American Society of Hematology published

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in 2011¹³: (a) newly diagnosed ITP, when patients had less than 3 months from diagnosis; (b) persistent ITP, when the time from diagnosis was between 3 and 12 months, including patients not reaching spontaneous remission or not maintaining complete response (CR) when therapy was discontinued; and (c) chronic ITP, when patients had shown the disease for more than 12 months.

All surgical procedures were performed in a right lateral decubitus using three or four trocars. The posterolateral ligaments of the spleen and the short gastric vessels were divided using ultrasonic energy. The splenic artery was ligated, and the splenic hilum was transected with a vascular stapler. Drains were used as necessary.

Patients were discharged from the hospital once they had recovered from surgery and were followed up in the outpatient clinic. Preoperative medications were tapered off and discontinued according to the level of platelets.

Results were evaluated at 1, 5, and 10 years after surgery. According to the standardized terminology developed by an international group and published by Rodeghiero et al.¹⁴ in 2009, response was classified into three groups: the CR group was defined as a platelet count of $\geq 100 \times 10^9/L$ in the absence of bleeding; the response (R) group was considered when the platelet count was $\geq 30 \times 10^9/L$ with at least a twofold increase of the baseline count, again without evidence of bleeding; and the no response (NR) group was determined when the platelet count was $< 30 \times 10^9/L$, when the increase from the baseline platelet count was less than twofold, or when patients experienced bleeding.

For the evaluation of potential prognostic factors, the following clinical and pathological variables were assessed: age, gender, preoperative platelet count, number of drugs used in the medical treatment, combination of immunosuppressors and corticosteroids, duration of preoperative therapy, the presence of accessory spleens at the time of splenectomy, the spleen's weight, and the platelet count during the first week after splenectomy. Bivariate and multivariate statistical analyses were used to assess all included variables. Statistical tests were applied according to each particular variable scaling: *t* test for dimensional variables, Mann-Whitney U for ordinal variables, and chi-squared test for dichotomic variables. Nonparametric test were performed whenever the variable distribution was observed as non-normal. Any *P* value $\leq .05$ for a two-tailed distribution was considered as statistically significant. The analyses were performed using SPSS version 20.0 software (SPSS, Inc., Chicago, IL) and Excel[®] from Microsoft[®] (Redmond, WA) Office.

TABLE 1. PATIENT CHARACTERISTICS

Characteristic	Value
Male/female (<i>n</i>)	42/108
Age (years)	37.3 ± 15.8
Preoperative platelet count (cells/mL)	70,790 ± 73,800
Duration of preoperative treatment (months)	32 ± 48.5
Blood transfusion [<i>n</i> (%)]	8 (5.3)
Spleen weight (g)	122.5 ± 72
Accessory spleen [<i>n</i> (%)]	10 (6.6)

Data are mean ± standard deviation values unless otherwise indicated.

TABLE 2. CLINICAL RESPONSE TO SPLENECTOMY AT 1, 5, AND 10 YEARS

Clinical response	1 year (<i>n</i> = 150/150) ^a	5 years (<i>n</i> = 57/86) ^a	10 years (<i>n</i> = 18/40) ^a
Complete response	133 (88.7%)	48 (84.2%)	15 (83.3%)
Response	4 (2.7%)	5 (8.8%)	1 (5.6%)
No response	13 (8.6%)	4 (7%)	2 (11.1%)

Data are number (%).

^aNumber of patients followed up/total number of patients with that follow-up.

Results

There were 108 (72%) women and 42 (28%) men with a mean age of 37.3 ± 15.8 years. The mean preoperative platelet count was 70,790 ± 73,800 cells/mL. A group of 91 (60%) patients received prednisone at a dose of 1 mg/kg/day as initial treatment. Only 52 (34.7%) of the patients received corticosteroids as the only drug. In 98 (65.3%) of the patients, corticosteroids were administered in addition to androgens, immunosuppressors, and/or immunoglobulin G. The mean duration of preoperative treatment was 32 ± 48.5 months.

The most common surgical indication was refractory disease, which was the case in 104 patients (69.3%). Recurrent disease was the surgical indication in 43 patients (28.7%), and adverse effects of steroids were the cause in 3 (2%). Operative time was 2.17 ± 0.70 hours, and average blood loss was 171 ± 185 mL. Mean hospital stay was 3.8 ± 2.1 days. Table 1 summarizes the general characteristics of our patient population. Surgical complication was documented in 5 (3.3%) patients because of bleeding at the surgical site. Three cases required laparoscopic exploration.

Clinical response at 1, 5, and 10 years after splenectomy is summarized in Table 2. During the first postoperative year, 133 (88.7%) cases were in the CR group, 4 (2.7%) were in the R group, and 13 (8.6%) were in the NR group. Analysis of response according to the length of the disease is shown in Table 3.

Platelet count reached a level of $\geq 150,000$ cells/mL during the first postoperative week in 104 patients, and they were considered immediate responders. At 1 year after surgery 94.2% of the immediate responders versus 76.1% of patients who did not have immediate response

TABLE 3. RESPONSE AT 1 YEAR AFTER LAPAROSCOPIC SPLENECTOMY CLASSIFIED BY IMMUNE THROMBOCYTOPENIA DURATION

Degree of response	Newly diagnosed ITP	Persistent ITP	Chronic ITP
CR	21 (91.3%)	48 (88.9%)	64 (87.7%)
R	1 (4.3%)	0	3 (4.1%)
NR	1 (4.3%)	6 (11.1%)	6 (8.2%)

Data are number (%). All comparisons between groups gave *P* = not significant.

CR, complete response; ITP, immune thrombocytopenia; NR, no response; R, response.

TABLE 4. IMPACT OF INITIAL RESPONSE ON THE LONG-TERM DEGREE OF RESPONSE

Initial response (cells/mL)	1 year (n=113/113) ^a			5 years (n=57/86) ^a			10 years (n=18/40) ^a		
	CR	R	NR	CR	R	NR	CR	R	NR
Present at $\geq 150,000$ (n=104)	98 (94.2)	1 (1)	5 (4.8)	27 (84.4)	2 (6.2)	3 (9.4)	5 (71.4)	0 (0)	2 (28.6)
Absent at $< 150,000$ (n=46)	35 (76.1)	3 (6.5)	8 (17.4)	21 (84)	3 (12)	1 (4)	10 (90.9)	1 (9.1)	0 (0)
	P=.001			P=NS			P=NS		

Data are number (%)

^aNumber of patients followed up/total number of patients with that follow-up.

CR, complete response; NR, no response; NS, not significant; R, response.

were in the CR group ($P=.005$). This difference did not reach statistical significance at 5 and 10 years (Table 4). Immediate responders also had a higher platelet count 1 year after surgery than the non-immediate responders (275,100/mL versus 186,000/mL, respectively) ($P<.0001$). This difference did not persist in the evaluation at 5 and 10 years.

Differences in response were also evaluated according to the surgical indication. There were no statistical differences in the degree of response 1 year after LS in the patients who underwent LS due to recurrent ITP or refractory ITP or in those who experienced adverse effects to the steroids (Table 5). The analysis of other potential prognostic factors for clinical response at 1 year is shown in Table 6. From all variables included in the multivariate analysis, none was statistically significant. A multivariate regression analysis was also performed to assess potential prognostic indicators for immediate response to LS. Age and the preoperative platelet count proved statistically significant ($P=.001$ and $P=.01$, respectively).

Discussion

Since the publication by Delaitre and Maignien¹⁵ in 1991, LS has been widely used in many hematological diseases, especially in ITP. Splenectomy is considered a second-line treatment for ITP patients mainly in refractory to medical therapy. Response of ITP after splenectomy, either open or laparoscopic, is usually very high, with an incidence of surgical failure as low as 5%.^{5,6} Vecchio et al.¹⁶ demonstrated similar rates of CR after LS and open splenectomy (80% versus 85%, respectively) in 40 patients with ITP. Liu et al.¹⁷ in a similar fashion did not find statistical difference between the two approaches in a series of 54 patients with

ITP (66.7% laparoscopic versus 70.8% open, $P=.74$). Results in our series of 150 patients who underwent LS for ITP were 88.7% in the CR group and 2.7% in the R group, which gives 91.4% of any degree of response.

LS has been considered the standard approach for patients with refractory or recurrent ITP requiring spleen removal. This is based on a similar cure rate with lower frequency of complications than open splenectomy. In a systematic review including 3385 patients with ITP, Kojouri et al.¹⁸ reported a complication rate of 9.6% in the group of patients who underwent LS, a value significantly less than the 12.9% associated with open splenectomy. The complication rate found in our series was 3.3%. This is in accordance to the $<5\%$ rate reported by high-volume centers.¹⁹

As in any other disease, there has been great enthusiasm in identifying potential indicators that may predict success of LS in ITP. Immediate response to splenectomy has been evaluated as potential prognostic indicator of long-term response, and different cutoff values have been suggested. Ojima et al.⁶ found that a platelet count of $\geq 150,000$ cells/mL 1 week after surgery was associated with CR or partial clinical response, 2–10 years after splenectomy in 75% of the patients. In a similar study, Wu et al.¹⁹ found that a platelet level of $\geq 100,000$ cells/mL within 1 month after splenectomy accurately predicted successful clinical response up to 4 years. In our series, initial response to splenectomy correlated with a higher frequency of CR and a higher platelet count 1 year after surgery when compared with the patients who did not have a good initial response ($P=.001$). These differences did not persist in the evaluation at 5 and 10 years. Potential explanation to the lack of significant differences in the long term may be the reduced number of patients who persisted under surveillance in the long term.

Several studies^{8,20} have demonstrated that patients older than 50 years have a lesser frequency of CR compared with younger individuals. On the other hand, preoperative platelet count has been also evaluated as potential prognostic factor of response. Duperier et al.⁸ demonstrated that a preoperative platelet count of $>70,000$ cells/mL predicted satisfactory clinical response of splenectomy in some ITP patients. However, other studies such as the one published by Balagué et al.¹¹ were unable to confirm the importance of the preoperative platelet count on clinical response. We were unable to demonstrate a significant prognostic factor other than a rapid postoperative recovery for CR 1 year after surgery. However, results of a subanalysis demonstrated that younger age and higher preoperative platelet count predicted immediate response (a platelet count of $\geq 150,000$ cells/mL at 1 week

TABLE 5. RESPONSE 1 YEAR AFTER LAPAROSCOPIC SPLENECTOMY CLASSIFIED BY SURGICAL INDICATION

Surgical indication	CR	R	NR
Refractory ITP	90 (67.7)	4 (100)	10 (76.9)
Recurrent ITP	40 (30.1)	0	3 (23.1)
Adverse effect of steroids	3 (2.3)	0	0

Data are number (%). All comparisons between groups gave P =not significant.

CR, complete response; ITP, immune thrombocytopenia; NR, no response; R, response.

TABLE 6. ANALYSIS OF POTENTIAL PROGNOSTIC FACTORS OF RESPONSE OF LAPAROSCOPIC SPLENECTOMY AT 1 YEAR

	CR (n=133)	R (n=4)	NR (n=13)	P
Male/female (n)	39/94	0/4	3/10	.4
Age (years)	36.6±16	48.0±10.6	40.8±13.9	.26
Preoperative platelet count (cells/mL)	72.6±76.0	19.0±13.7	67.4±56.0	.35
Drugs used before surgery (n)	1:46	1:1	1:4	.66
	2:60	2:3	2:6	
	>2:27	>2:0	>2:3	
Use of corticosteroids plus immunosuppressors (n)	72 (54.1%)	1 (25%)	6 (46%)	.56
Duration of preoperative therapy (months)	32.5±50.3	42.7±45	27.4±28.7	.85
Spleen weight (g)	124.2±73	127±64.8	98.2±58.3	.58
Presence of accessory spleen (n)	10 (6.6%)	0	0	.5

CR, complete response; NR, no response; R, response.

postoperatively). Therefore, age and preoperative platelet count consequently could have an indirect association with CR at 1 year.

Tsereteli et al.,⁹ among others, have suggested that a shorter time between the diagnosis and the time of splenectomy correlates with a better prognosis. Based on the classification proposed by the American Society of Hematology¹³ that divides ITP into newly diagnosed, persistent, and chronic, we did not find any difference in the response rate between the groups.

The lack of demonstration of potential prognostic factors of long-term response after LS in patients with ITP in this study may be related to several factors. One is the definition of success. Previous evaluations have been performed using different criteria for cure. Another is the number of patients included in our study, which may be too small for the proper identification of the prognostic factors. Subsequent studies using the new definitions included in this study will be needed to assess potential prognostic factors of success in patients with ITP after laparoscopic surgery.

Disclosure Statement

No competing financial interests exist.

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