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Laparoscopic splenectomy for second-line treatment of immune thrombocytopenia – analysis of 53 patients and current perspectives

Laparoscopic splenectomy for immune thrombocytopenia

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Summary
Background Splenectomy is a well-established second-line treatment for immune thrombocytopenia but novel medical therapies have changed the management of this disease. The objective of this study is to analyze the current results of splenectomy as a second-line treatment.
Methods Retrospective analysis of 53 consecutive patients with chronic immune thrombocytopenia submitted to splenectomy from January 2007 through December 2014. Several parameters were analyzed including postoperative morbidity and outcomes after surgery.
Results Fifty-two (98%) patients underwent successful laparoscopic splenectomy without conversion to open procedure, with a mean operative time of 103.6 ± 38.1 minutes. The median postoperative length of stay was 3 days (range 1–36 days). There were 3 (5.7%) major postoperative complications resulting in 2 (3.8%) reoperations. No splenectomy-related mortalities occurred. Fifty (94.3%) patients presented a response 1 month after surgery (45 complete responses and 5 responses). In the follow-up (mean 24.8 ± 16.9 months) 37 (75.5%) patients had a complete and sustained response after laparoscopic splenectomy and an additional 11 (22.4%) presented platelet counts above 30×10^9/L (the majority of these patients eventually reaching normal platelet counts). No additional therapies were needed in 39 (79.6%) patients after surgery.
Conclusions In our experience, laparoscopic splenectomy is an effective second-line treatment for Immune Thrombocytopenia with short and long-term response rates of 94% and 91%, respectively. Major postoperative complications occurred in 6%. Future research should aim to discover new methods to properly select patients to different second-line treatments.

Keywords Laparoscopy · Splenectomy · Immune Thrombocytopenia · Treatment · Outcomes

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Background

Immune thrombocytopenia (ITP) is an autoimmune disorder defined by an isolated decrease of platelet count ($< 100 \times 10^9$/L) resulting from accelerated clearance and destruction of antibody-coated platelets by tissue macrophages, predominantly in the spleen. In Europe, the annual incidence is estimated to be around 3 per 100.000 people, affecting predominantly male children and middle-aged adult women [1].

Splenectomy is a second-line treatment for adult ITP and should be considered whenever steroid-based therapy fails to achieve or sustain remission, or is intolerable for the patient due to severe adverse reactions.

The recent advent of new drugs for the treatment of ITP, namely anti-CD20 antibodies (Rituximab) and thrombopoietin receptor agonists (TPO-RA) have questioned the role and timing of splenectomy as second line treatment for ITP. A number of other

Tab. 1 Gender, age and ASA score of the studied population

Gender	
Female	34 (64.2)
Male	19 (35.8)
Age	
Mean	45.0 (± 16.3) Years (± standard deviation)
Median	48.0 (17–76) Years (minimum-maximum)
ASA score	
1	9 (17.0)
2	33 (62.3)
3	11 (20.8)

Values in parentheses are percentages unless indicated otherwise.

medications are prescribed off-label to treat ITP with varying degrees of evidence and efficacy [2].

Furthermore, an increased awareness of late remissions by physicians and patients, the inability to predict response to surgery and the rare but dramatic complications related to splenectomy have encouraged a generalized tendency to choose some sort of medical therapy for second-line treatment of ITP. As a result, a 50 % decrease in the rate of splenectomy (from 50–60 % in previously reported cohorts to 20–25 % more recently) in patients with ITP was observed [3].

However, with progress in minimally invasive surgery and perioperative care, the safety profile after splenectomy may presently be superior to those reported in historical series. There is a clear evidence that splenectomy continues to provide a high and sustained cure rate and should not be delayed to third line "salvage" therapy.

Studies comparing different second-line medical therapies and splenectomy are lacking, and long-term results and complications of recent medical therapies are yet to be completely established. A 2010 international consensus statement [4] ranked splenectomy as similar to a number of treatments, whereas the American Society of Hematology guidelines [5] accorded to splenectomy its highest grade of recommendation based on its curative effects and the extensive published experience.

In order to adequately consider ITP response and morbi-mortality after splenectomy, the description of the current state-of-the-art results is needed so that its risk/benefit ratio can be compared to the newest medical treatments. The primary objective of this study is to analyze the results of splenectomy (postoperative morbidity and outcomes) and to discuss the modern place for laparoscopic splenectomy in the treatment of patients with ITP. Our results support that splenectomy is a safe and effective second-line treatment for ITP.

Methods

All adults (≥ 18 years old) submitted to splenectomy as a primary elective procedure have been included in an electronic database since January 2007: in December 2014 there were 42 patients submitted to open splenectomy and 108 patients submitted to laparoscopic splenectomy. This database was retrospectively reviewed for patients with ITP who underwent splenectomy and the medical records were analyzed.

The definition and diagnosis of ITP was established according to a report from an international working group [6], which included isolated thrombocytopenia (< 100 × 10^9/L), otherwise normal findings on a peripheral blood smear, normal bone marrow aspirate, and no other associated benign or malignant diseases that could have induced thrombocytopenia. Chronic ITP was defined as isolated thrombocytopenia lasting for more than 12 months.

The following variables were studied: demographics, first line therapies, indication for splenectomy, spleen weight, pre and postoperative platelet count, surgery duration, number of trocars used, abdominal drainage, associated procedures, the presence of accessory spleens, conversion to laparotomy, major post-operative complications defined as grade ≥ 3 according to the Clavien–Dindo classification [7], post-operative and long term mortality, response after splenectomy, use of additional medical therapies after surgery, and months of follow-up after surgery.

Response after splenectomy was defined as follows [6]: complete response (CR): platelet count ≥ 100 × 10^9/L and absence of bleeding; response (R): platelet count ≥ 30 × 10^9/L and, at least, a twofold increase in the baseline count, and absence of bleeding; no response (NR): platelet count < 30 × 10^9/L or less than twofold increase of baseline platelet count or bleeding. Loss of CR or R was also defined as platelet count below 100 × 10^9/L or bleeding (from CR) or below 30 × 10^9/L or less than twofold increase of baseline platelet count or bleeding (from R). An assessment of the response was made at 1 and 6 months after surgery and subsequently monitored in the follow-up.

All statistical analyses were performed using IBM SPSS Statistics, version 23.0 (Chicago, IL, www.spss.com).

Results

Over the 8-year study period, 53 adult patients were submitted to splenectomy as a second-line treatment for ITP. There were 34 (64.2 %) female and 19 (35.8 %) male patients (male to female ratio: 0.56). The mean age was 45.0 ± 16.3 years. Regarding the American Society of Anesthesiologists (ASA) score, 42 (79.2 %) patients presented none or mild systemic diseases (ASA score 1 or 2) – Tab. 1.

All patients experienced chronic ITP with minimum platelet counts inferior to 30 × 10^9/L and all received

Tab. 2 Major postoperative complications and treatment required

Complication	Clavien	Treatment	Discharge
Intra-abdominal collection and Pneumonia	IIIa	Percutaneous drainage and antibiotics	26 days after surgery
Major vessel injury by Veress needle	IIIb	Hemostasis by laparotomy 6 hours after initial surgery	3 days after surgery
Pancreatic fistula and multiorgan dysfunction syndrome	IVb	Laparotomy for adequate drainage, Intensive Care Unit	36 days after surgery

Tab. 3 Response and additional medical therapies after splenectomy

1 Month after LS	6 Months after LS	Follow up (median 20 months)	Monotherapy after surgery[a]	Multitherapy after surgery[a]
CR 45 (81.1 %)	37 CR	37 CR	1+1	
	4 loss of CR	1 NR[b]		1
		3 CR	1 +1[c]	1
	4 patients abandoned follow up			
R 5 (9.4 %)	2 CR	2 CR	1	
	3 R	1 CR		
		2 R		
NR 3 (5.7 %)	1 CR	1 CR	1	
	2 NR	2 CR	1	1

[a] Not accounting for tapering of perioperative steroids
[b] Death 2 years after surgery due to intracerebral hemorrhage
[c] Refused steroid therapy: Romiplostim was used for 1 year after surgery then discontinued with sustained CR

corticosteroids as first line therapy: the most used regimen, in 44 (83.0 %) patients, was oral prednisone 1–2 mg/kg/day for induction (therapeutic purposes) and then a maintenance dosage of < 1 mg/Kg/day. Intravenous immunoglobulin was used in 34 (64.2 %) patients, 1 g/Kg/day for 2 consecutive days to treat acute bleeding not responding to steroids. Indications for splenectomy were unresponsiveness to steroid therapy in 37 (69.8 %) patients, intolerance or major adverse side effects of steroid therapy in 11 (20.8 %), refusal of steroid therapy in 3 (5.7 %) and disease relapse after more than 5 years of steroid therapy in another 2 (3.8 %) patients.

Vaccination against *Streptococcus pneumoniae, Neisseria meningitidis*, and *Haemophilus influenza* was administered to all patients at least 2 weeks before surgery. Intravenous immunoglobulin (1 g/Kg/day) was used in all patients for 2 days before surgery, and the median preoperative platelet count after this treatment was 87 × 10^9/L (range 21–224 × 10^9/L). Standard perioperative thromboprophylaxis (enoxaparin 0.5 mg/Kg/day) was administered to all patients.

Fifty-two patients (98 %) underwent successful laparoscopic splenectomy without conversion to open procedure. The median number of trocars used was 4 (range 3–5). The mean operative time was 103.6 ± 38.1 min, measured from the beginning of pneumoperitoneum to skin closure. Five (9.4 %) patients had associated procedures (oophorectomy in one patient, tubal ligation in another patient, and cholecystectomy in three patients). The mean splenic weight was 163.7 ± 70.4 g and accessory spleens were identified and removed in 7 (13.2 %) patients. An endostapler was used in 37 (69.8 %) patients for vascular ligation, either alone or in association with other vascular ligation techniques. In 34 (64.2 %) patients the spleen was intentionally fragmented before removal in order to facilitate extraction and to reduce the incision length. An abdominal drain was placed in 11 (20.8 %) patients.

The median postoperative length of stay was 3 days (range 1–36 days). The three (5.7 %) major postoperative complications are presented in Tab. 2 and resulted in 2 (3.8 %) reoperations. No splenectomy-related 30-day mortalities occurred.

Four patients (7.5 %) were lost to follow-up (two patients at 1 month and two patients at 3 months after surgery). For the remainder 49 patients, the mean follow-up was 24.8 ± 16.9 months (median 20.0 months, range 5–66).

Response after splenectomy is resumed in Tab. 3. At 1 month after surgery, 50 (94.3 %) patients had obtained a response (45 CR and 5 R).

In patients with CR 1 month after surgery (45–84.9 % – patients), 37 (75.5 %) had a sustained CR at long term follow up, 4 had loss of CR; 3 re-achieved CR after medical therapy, and 1 patient maintained platelet counts < 30 × 10^9/L despite several medical therapies and died 2 years after surgery due to intracerebral hemorrhage. Four other patients in this group abandoned follow-up.

In patients with R 1 month after surgery (5–9.4 %), two achieved CR 6 months after surgery (only one patient needed steroid therapy) and one achieved CR after 1 year. The other two maintained platelet counts between 30–100 × 10^9/L.

In the three (5.7 %) patients with NR 1 month after surgery, one achieved CR 6 months later and the other two achieved CR 1 year after surgery, nevertheless requiring corticoid therapy.

Considering the 49 patients with a long-term follow up, splenectomy resulted in CR in 46 (93.9 %), R in 2 (4.1 %), and NR in another 1 (2.0 %). No additional therapy was needed in 39 (79.6 %) patients after surgery besides tapering of perioperative steroids; single therapy was used in 7 (14.3 %) patients – steroids in 6 and Romiplostim in 1 – and several medical therapies were used in 3 (6.1 %) patients with NR after splenectomy (Fig. 1). As previously mentioned, only one (2,0 %) patient died on long term follow up due to intracerebral hemorrhage 2 years after surgery.

Conclusions

Significant advances in the understanding of ITP pathogenesis have been made during the past decades,

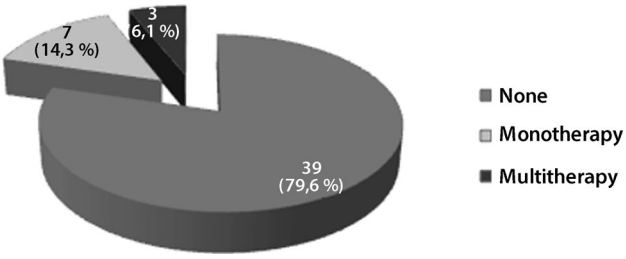

Fig. 1 Additional therapies after splenectomy

leading to the development of novel treatments, namely Rituximab and TPO-RA. This has resulted in an increased uncertainty as to the place of splenectomy in the management of ITP; the results presented in this study support that splenectomy is a safe and effective second-line treatment for ITP.

Whenever surgery is indicated laparoscopic splenectomy is the "gold-standard" [8] presenting several advantages when compared to open splenectomy: decreased postoperative pain, fewer wound infections and other abdominal wall related complications, shorter hospital stay and more rapid return to work, all of which contribute to lower costs. The well-characterized safety profile and generally preventable complications of laparoscopic splenectomy implies surgical expertise, proper patient selection and perioperative preparation including the preoperative optimization of the platelet count, adequate vaccination, and judicious use of antibiotics and thromboprophylaxis.

In our series 98 % of splenectomies were performed by a laparoscopic approach without conversion to open surgery. Our results confirm the benefits of minimally invasive surgery: short hospital stay (median 3 days), few (< 10 %) major complications (particularly no abdominal wall-related complications), and no surgery-related mortality. The operative time was not excessive (with a mean of approximately 100 min), other procedures could be associated, and accessory spleens were identified in 13.2 % patients as expected.

Regarding the efficacy of splenectomy in the treatment of ITP, in our series 50 (94.3 %) patients had a short-term response. At long-term follow-up 37 (75.5 %) patients had a complete and sustained response and an additional 11 (22.4 %) patients presented platelet counts above 30×10^9/L – this heterogeneous group included patients with R as defined above and patients with loss of CR requiring further medical therapy. The majority of these patients (9 patients) eventually achieved normal platelet count at long-term follow-up. No additional therapies were needed in 39 (79.6 %) patients after surgery. Only three (6.1 %) had NR to laparoscopic splenectomy, and one of them eventually died from non-surgical related hemorrhagic complications.

Mikhael et al. [9], based on their systematic review of 23 published articles between 1997 and 2007 including 1223 laparoscopic splenectomies for the treatment of ITP, performed across 13 countries, reported a short-term failure rate of 8.2 %. Furthermore, the long-term relapse rate was 43.6 per 1000 patient-years of follow up, which translates to approximately a 28 % failure rate after 5 years for all patients. As described in other studies [10–12] 60–66 % of patients remain in clinical remission at long-term follow-up after splenectomy, an outcome unmatched by any other therapy. Furthermore responding patients require a straightforward follow-up. These results clearly contrast with those reported for Rituximab (e. g., CR falls to ~20 % by 2–5 years after a single course) and TPO-RA (e. g., healthcare professional required to administer Romiplostim, and frequent monitoring of liver function tests for eltrombopag). A recent study [13] reported that Rituximab had an overall response rate of 81 % but 68 % of patients eventually relapsed.

As mentioned in a European multicentric study [14] of 233 ITP patients who underwent splenectomy between 1959 and 2001, with a minimum post-operative follow-up of 10 years, long term complications such as infectious diseases, hemorrhagic events, and thrombosis mainly affected non-responding patients and were fatal in a minority of the cases. A stable response to splenectomy was associated with a lower rate of infections and hemorrhage.

Patient selection is, therefore, critical when considering the different second-line modalities for IPT [15]. Splenectomy may be strongly considered for younger patients (those who present the best response and lower postoperative complication rates), women who contemplate pregnancy (other therapies may not be safe for the fetus), patients with a high risk of inevitable trauma related to professional activities, and patients potentially noncompliant or not willing to accept daily and sometimes lifelong treatments, frequent follow-up consultations and lifestyle changes. However, in older patients, those with severe comorbidities, chronic exposure to infections cleared by the spleen (e. g., malaria or babesia) or high risk of thrombosis, splenectomy should be regarded as a high-risk treatment and other options may be more suitable in this setting. All treatment options should be clearly discussed in a personalized and unbiased way with each patient and participating family members, as the choice will also be influenced by psychosocial factors.

Other methods of splenic tissue eradication, such as partial splenic embolization and splenic irradiation, might be possible treatment options, particularly in patients with co-morbidities that preclude surgery. These techniques are not widely available and expertise is lacking, but moderate success (with a minority of patients attaining complete responses) at the expense of reasonable morbidity and no mortality have been reported [16].

Predicting response to splenectomy is not possible using readily available clinical criteria other than older

age [10]. In a retrospective review [17] of ^{111}In-labeled autologous platelet sequestration studies, the CR rate after splenectomy was 87 % in patients having predominantly splenic sequestration, compared to 35 % in patients with "mixed" or hepatic sequestrations. Technical difficulties and limited availability were the key limitations and confirmatory studies are needed. However, if response to splenectomy becomes predictable based on a widely available and reliable test, then it could be possible to improve a proper patient selection.

In conclusion, laparoscopic splenectomy is a safe and effective second-line treatment for patients with ITP and it remains a central therapy in this setting. Recent medical therapies should not lessen its importance. Future research should aim to discover new methods to properly select patients for the expanding variety of second-line treatments.

Conflict of interest A. Costa-Pinho, D. Fernandes, R. Bessa-Melo, M. Aral, L. Graça and J. Costa-Maia declare that there are no conflicts of interest.

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