Indian Journal of Surgery (December 2022) 84(6):1205–1210
https://doi.org/10.1007/s12262-021-03206-1

ORIGINAL ARTICLE

Splenectomy for Acute or Persistent Immune Thrombocytopenia: an Overkill or a Necessity

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Received: 2 July 2021 / Accepted: 4 December 2021 /Published online: 16 January 2022

Abstract

Splenectomy is usually deferred for the first 12 months of onset of immune thrombocytopenia (ITP) because patients may have spontaneous remission. However, in patients with failed medical management, splenectomy is a valuable treatment option. This study aimed to evaluate the role of splenectomy in patients with persistent ITP with failed medical management at a tertiary care center. A retrospective review of records of all patients who underwent splenectomy for ITP between January 2010 and December 2019 was done. We identified the patients with primary ITP refractory to medical management who were referred from hematology to our department for splenectomy and their clinical course was evaluated. Most of the patients were females (14/20, 70%), and the mean age of patients in our series was 33.7 ± 11.1 years. Skin petechiae and mucosal bleeding were the most common presenting symptoms. Mean pre-operative platelet count was 20,079 ± 11,644/μL. After a trial of medical management for a mean duration of 6.7 ± 3.6 months, patients were planned for splenectomy. All patients improved symptomatically after surgery. A significant increase in platelet count was observed (mean: 80,290 ± 75,327/μL). Splenectomy (either open or laparoscopic approach) is a safe and very good option in patients with new onset and persistent ITP refractory to medical management with favorable outcomes.

Keywords Spleen · Splenectomy · Acute ITP · Newly diagnosed ITP · Persistent ITP · Laparoscopic splenectomy

Introduction

In 1916, first successful splenectomy for immune thrombocytopenia (ITP) was performed in a 36-year-old female [1]. Since then, management of ITP has evolved with a more comprehensive understanding of pathophysiology and introduction of newer drugs targeting different pathways. Despite these advances, splenectomy has stood the test of time and is an important option in the management of primary ITP. In approximately 80% of patients, a good response after splenectomy is seen with a long-term success rate of up to 50–70% [2]. Splenectomy is deferred in the first 12 months of diagnosis, but in patients with drug refractory ITP, splenectomy is a valuable treatment alternative [3]. This study conducted at a tertiary health care center aimed to review operative outcomes of splenectomy in patients with newly diagnosed and persistent ITP refractory to medical management.

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Patients and Methods

It is a single-center retrospective study of patient with drug refractory acute or persistent ITP who underwent splenectomy at a tertiary care center.

A cohort of 20 patients with newly diagnosed or persistent ITP who underwent splenectomy at our institute between January 2010 and December 2019 and had a minimum follow-up of 12 months was included.

The diagnosis was made on the basis of patient's history, physical examination, complete blood count, and peripheral smear. All patients received steroids (Prednisolone) in the pre-operative period and 13 patients received steroids in combination with other drugs, viz. intravenous immunoglobulin (IVIg) (0.83 g/kgwt), Dapsone (50–100 mg per day), anti-CD20 monoclonal antibodies Rituximab (375 mg/m^2 once weekly/4 weeks), and Eltrombopag (50 mg once daily for 4 weeks). Steroids were started at a standard dose of 0.5–2 mg/kg/day. If no significant rise in platelets count was seen after 4 weeks, then the dose was tapered. The patients who received medical treatment were monitored for 4 weeks and the patients with major bleeding according to Updated International Consensus Report 2019 who did not respond to medical management were then referred to our department for splenectomy [4].

All patients underwent ultrasonographic examination and received vaccination in the pre-operative period. The vaccination was done against the Hemophilus Influenzae, pneumococcal, and meningococcal organisms at least 4 weeks prior to surgery. Splenectomy was performed by either open or laparoscopic approach. An upper midline laparotomy was done for open splenectomy. For laparoscopic splenectomy, a standard four ports technique was used. Accessory spleens were looked for in each patient and drain was placed in all the patients. After the patients recovered from surgery, they were discharged from the hospital and were followed up in outpatient department. All patients received antibiotic prophylaxis (Amoxycillin 500 mg twice/day) in the post-operative period for 12 months. Patients were assessed at 1 week and at 12 months for signs and symptoms of bleeding and platelet counts. We usually follow these patients at 1 week and at 12 months and advise them to visit the emergency department in case of any acute exacerbation of bleeding manifestations in between 1 week and 12 months period.

The following clinical and pathological variables were assessed: age, sex, presenting complaints, duration of symptoms, pre-operative platelet count, number of drugs received (steroid, IVIg, Dapsone, Rituximab, Eltrombopag), presence of accessory spleen, weight of the spleen, platelet counts after 1 week and 12 months of splenectomy, and clinical manifestations of thrombocytopenia if any in the form of mucosal bleed like epistaxis, gum bleed, and melena.

Definitions

On the basis of American Society of Hematology guidelines 2019, the patients were categorized into three groups, (a) Newly diagnosed ITP: ITP duration of < 3 months, (b) Persistent ITP: ITP duration of 3–12 months, Chronic ITP: ITP duration of > 12 months [3]. Patients with newly diagnosed or persistent ITP were included in this study.

The response was assessed and classified according to American Society of Hematology guidelines 2019 into early response which was defined as platelet count ≥ 30,000/μL and at least doubling baseline at 1 week and remission which was defined as platelet count ≥ 100,000/μL and at least doubling baseline at 12 months [3]. The response was also categorized by the International Working Group's definition of response into no response, response, and complete response [5]. No response was defined as any platelet count lower than 30,000/μL or less than twice the baseline. Response was defined as any platelet count between 30,000 and 100,000/μL or and at least two times the baseline value of platelet count with concurrent resolution of symptoms. Complete response was defined as a platelet count of 100,000/μL or more. Bleeding event was defined according to Updated International Consensus Report 2019 [4].

Statistical Analysis

The various parameters were classified into continuous or discrete variables. For the continuous variables, mean and standard deviation was calculated. For the nominal or qualitative variables, frequencies and percentages were calculated. Quantitative data (platelet count and increase in platelet count) was compared using Mann–Whitney's test and Fisher's exact test was used to compare qualitative data (response to splenectomy). Correlation between response to splenectomy and baseline characteristics, viz. age, pre-operative platelet count, and duration of symptoms, was assessed by univariate logistic regression. All statistical analyses were performed using Stata version 16 (StataCorp 2019, College Station, Texas).

Results

Baseline Characteristics

The study population was comprised of 14 females (70%) and 6 males (30%) with a median age of 32 years (18–60 years). The mean pre-operative platelet count was 18,410 ± 11,614.9/μL. Skin bleeding manifestations like petechiae and mucosal bleeding (gum bleed or epistaxis) were present in all the patients. At least one episode of GI

bleed (melena) was reported by nearly half of the patients (9/20, 45%). Female patients also reported menorrhagia as one of the presenting complaints. It was present in 71.4% of the females. All patients had received a trial of steroids (Prednisolone) (20/20,100%) but failed to show an early or durable response. Forty percent of patients had also received a trial of intravenous immunoglobulins (IVIg). Dapsone (6/20, 30%), anti-CD20 monoclonal antibodies, i.e. Rituximab (5/20. 25%), and TPO receptor agonist—Eltrombopag (4/20, 20%) were other commonly used drugs. Table 1 summarizes the baseline characteristics of all patients included in the study.

Operative Details and Outcome

Splenectomy was performed in these patients (open approach-13 and laparoscopic approach-7). Accessory spleen was identified in one patient with newly diagnosed ITP. No inadvertent injury (e.g., bowel injury, renal injury diaphragmatic injury) was reported in our patients. Seventy percent of patients required intra-operative Single Donor Platelet (SDP) transfusion. Twenty percent of patients needed SDP transfusion in post-operative period. Twenty-five percent of patients also received Packed Red Blood Cells (PRBC) transfusion during surgery. Average post-operative stay was 4.3 (± 1.9) days. Four patients had surgical site infection in post-operative period. One patient had intra-abdominal collection which was managed by ultrasonographic-guided percutaneous single time aspiration. No bleeding occurred in post-operative period in any patient. Table 2 summarizes the intra-operative and post-operative findings in the patients.

Table 1 Summary of baseline characteristics of all patients included in the study

Characteristics	Total ($N=20$)
Age (years, median and range)	32.5 (18–60)
Male:female	6:14
Mean duration of symptoms (months, mean)	6.7 (± 3.5)
Mean pre-operative platelet count (/μL, mean)	18,410 ± (11,614.9)
Symptom (*n*, %)	
1. Petechiae	20 (100%)
2. Mucosal bleed-gum bleed, epistaxis	20 (100%)
3. GI bleed-melena, hematemesis	9 (45%)
4. Menorrhagia (females)	10 (71.4%)
5. Bleeding requiring transfusion	5 (25%)
Drug (*n*, %)	
1. Steroid	20 (100%)
2. IVIg	8 (40%)
3. Rituximab	5 (25%)
4. Eltrombopag	4 (20%)
5. Dapsone	6 (30%)

Hematological and Clinical Outcomes

Mean platelet count 1 week after surgery was 101,350 (± 73,708.4)/μL and 12 months after surgery was 10,7450 (± 62,587.1)/μL. All patients received 1 year of antibiotic prophylaxis post-surgery. Seventy-five percent of patients were off medication at the end of 1 year. There was no incidence of Overwhelming Post Splenectomy Infections (OPSI) reported in our series. Table 3 summarizes the hematological and clinical outcomes in patients.

Response

In our series, 65% of patients showed an early response to splenectomy and 55% of patients underwent remission. Table 4 summarizes the response and remission seen in patients.

The predictive factors for a successful splenectomy were assessed using both univariate and multivariate logistical regression. A significant correlation was seen between early response and remission at 1 year in our series (*p*-value 0.042). However, no correlation between early response was seen with patient's age (OR 0.965; 95% CI: 0.884–1.055), duration of symptoms (OR 1.103; 95% CI: 0.829–1.469), and pre-operative platelet counts (OR 1.000; 95% CI: 0.999–1.000). There was no association between remission and age (OR 1.021; 95% CI: 0.939–1.110), duration of symptoms (OR 0.949; 95% CI: 0.738–1.222), and pre-operative platelet counts (OR 0.999; 95% CI: 0.998–1.000).

Table 2 Summary of intra-operative and post-operative findings in patients

Variable	Total ($N=20$)
Laparoscopic:open	7:13
Mean operative time (min)	
Intra-operative SDP transfusion (*n*, %)	14 (70%)
Intra-operative PRBC transfusion (*n*, %)	5 (25%)
Incidence of accessory spleens	1 (5%)
Mean weight of spleen (grams, mean)	282.5 (± 148.8)
Post-operative SDP transfusion (*n*, %)	4 (20%)
Mean post-operative stay (days, mean)	4.3 SD 1.9
Morbidity	
1. Wound infection	4 (20%)
2. Intra-abdominal collection	1 (5%)
3. Bleeding	0 (0%)
4. Others	0 (0%)

Table 3 Summary of hematological and clinical outcomes in patients

Hematological and clinical outcomes	Total ($N=20$)
Mean platelet count at 1 week (/μL, mean)	101,350 (±73,708.4)
Mean increase in platelet count at one week (/μL, mean)	82,940 (±72,603.6)
Mean platelet count at 1 year (/μL, mean)	107,450(±62,587.1)
Mean increase in platelet count at 1 year (/μL, mean)	89,040 (±64,929.4)
Patients off medication	15 (75%)
Patients on steroid	5 (25%)
Patients on other drugs	-
OPSI (*n*/*N*, %)	-

Table 4 Summary of response and remission seen in patients

Response		Total ($N=20$)	*p*-value
At 1 week	Complete response	8 (40%	0.829
	Response	6 (30%)	
	No Response	6 (30%)	
Early response		*14 (70%)*	*0.613*
At 1 year	Complete response	11 (65%)	1.000
	Response	5 (25%)	
	No Response	4 (20%)	
Remission		*11 (65%)*	*1.000*

On multivariate logistical regression for same variables, no correlation was observed. Table 5 summarizes of correlation between patient's baseline characteristics and response or remission witnessed.

Discussion

After the first splenectomy was performed for a patient with ITP in 1916, it remained the only treatment option until 1951, when steroid therapy was introduced [1]. With a durable response in more than two-thirds of patients, splenectomy is still considered the mainstay of treatment [2]. Both American and British guidelines for ITP advocate deferral of splenectomy for at least 1 year after diagnosis [3, 6]. In our cohort of patients, 70% of patients showed an early response and at the end of 1 year, 65% patients underwent remission. The curative potential splenectomy offers are not achievable with any other modality. Role of splenectomy has been evaluated in patients with persistent and chronic ITP but its role in patients with newly diagnosed ITP remains unexplored.

Response rate with both open and laparoscopic splenectomy is comparable. However, laparoscopic splenectomy is emerging as a safe treatment alternative in patients with ITP. Kojouri et al. reported a complication rate of 9.6% with laparoscopic splenectomy which was significantly lower than complication rate seen with open splenectomy [7]. Thirty-five percent of our patients underwent laparoscopic splenectomy and had an uneventful post-operative recovery. Accessory splenic tissue can cause failure of splenectomy. Accessory spleens have been identified in 4–27% of open splenectomies and 11–21% of laparoscopic splenectomies [8–12]. We identified an accessory spleen in one of our patients (5%). Fibro-congestive changes in splenic parenchyma with maintenance of normal size and shape are seen in ITP. There was no incidence of splenomegaly and the mean weight of the spleen in our series was 282.5 g.

Unlike infiltrative bone marrow pathologies and aplasia, patients with ITP can tolerate markedly low platelet counts. However, severe bleeding can occur in patients with ITP especially at platelet counts less than 10,000/μL. Mortality rates of 0.4% and 1.6% attributed to bleeding have been reported in two case series [7, 13]. This however is an under-representation of an ITP severe enough to warrant

Table 5 Summary of correlation between patient's baseline characteristics and response or remission witnessed

Response	Independent variable	Odds ratio	*p*-value	95% CI
Early response	Age	0.965	0.436	0.884–1.055
	Pre-operative platelet count	1.000	0.352	0.999–1.000
	Duration of symptoms	1.103	0.500	0.829–1.469
Remission	Age	1.021	0.627	0.939–1.110
	Pre-operative platelet count	0.999	0.288	0.998–1.000
	Duration of symptoms	0.949	0.687	0.738–1.222
	Early response	12.5	0.042	1.089–143.432

splenectomy. Although splenectomy is generally regarded as a safe procedure, a case series has reported surgery-related death in 1.3% and surgery-related complications necessitating prolonged hospitalization and readmission in 26% of patients [7]. Another study has reported complication rate of 9.6% and 12.9% in laparoscopic and open splenectomy, respectively [7]. The long-term risks of sepsis and thrombosis are other major concerns in post-splenectomy patients [14]. Therefore, the risks and benefits of splenectomy are to be weighed carefully in each patient.

Remission rates of 60–90% have been reported in different studies [12, 15]. A systematic review has reported a complete response rate of 66% and a 5-year remission rate of 64% after splenectomy [16]. The rate of response did not change over time. In our series, 60% of newly diagnosed ITP patients and 53.3% of patients with persistent ITP achieved remission at the end of 1 year. There were another 20% patients in both the groups who achieved a favorable response.

Patients who showed an early increment in platelet counts at 1 week after surgery went into remission. A significant correlation was seen between early response and remission in our series (p-value 0.042). Numerous studies have assessed the correlation between different pre-operative and post-operative variables and response to splenectomy. Age at the time of splenectomy correlates most frequently with the response in existing literature. A systematic review found 14 studies that reported a better response in younger patients [16]. Although there was no specific age cut-off, a better outcome was seen in patients with mean or median age between 32 and 51 years compared with between 40 and 73 years [16]. Kumar et al. identified younger age and higher platelet count at the time of splenectomy as two pre-operative variables which were predictive of a favorable response to splenectomy [17]. In another study aimed to identify prognostic indicators for a successful laparoscopic splenectomy in ITP, young age and higher pre-operative platelet counts were suggestive of a favorable response [18]. In our study, there was no correlation between age of the patient and pre-operative platelet count with an early response or remission. No predictive role of duration of symptom has been identified in the literature. We also did not observe any significant correlation between resolution of symptoms and improvement in platelet count with duration of symptoms. Response to steroids is also reported to predict response to splenectomy. In a study by Mintz et al., remission rate was higher in patients who were responsive to steroids (92% vs 65%) [19].

The major limitations of this study are its retrospective nature, small study population, and short duration of follow-up. There are numerous studies defining the role of splenectomy in chronic ITP but there is paucity of literature assessing the role of splenectomy in newly diagnosed and persistent ITP. Our study aims to evaluate the role of splenectomy in such patients with an emphasis on factors predictive of a favorable response.

Conclusion

Splenectomy is a very effective treatment modality in patients with drug refractory ITP with a good and durable success rate. Although the peri-operative and long-term risks of splenectomy are low, the risks and benefits should be evaluated when surgery is planned. Prospective studies delving into indications of surgery, peri-operative management of newly diagnosed and acute ITP refractory to medical management, predictive factors for outcome, and long-term follow-up of such patients are warranted.

Data Availability Not applicable.

Code Availability Not applicable.

Declarations

Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Conflict of Interest The authors declare no competing interests.

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