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Laparoscopic splenectomy for primary immune thrombocytopenia: Current status and challenges

Dong Zheng, Chen-Song Huang, Shao-Bin Huang, Chao-Xu Zheng

Dong Zheng, Department of Hematology, the First Affiliated Hospital of Sun Yat-sen University, Guangzhou 510080, Guangdong Province, China

Chen-Song Huang, Shao-Bin Huang, Chao-Xu Zheng, Department of Pancreato-biliary Surgery, the First Affiliated Hospital of Sun Yat-sen University, Guangzhou 510080, Guangdong Province, China

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Correspondence to: Chao-Xu Zheng, MD, PhD, Professor of Surgery, Department of Pancreato-biliary Surgery, the First Affiliated Hospital of Sun Yat-sen University, 58 Zhongshan 2 Road, Guangzhou 510080, Guangdong Province, China. zhengchaoxu@yahoo.com
Telephone: +86-20-87755766-6214
Fax: +86-20-87750632

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Abstract

Primary immune thrombocytopenia (ITP) is an immune-mediated disorder affecting both adults and children, characterised by bleeding complications and low platelet counts. Corticosteroids are the first-line therapy for ITP, but only 20%-40% of cases achieve a stable response. Splenectomy is the main therapy for patients failing to respond to corticosteroids for decades, and about two-thirds of patients achieve a long-lasting response. Although some new drugs are developed to treat ITP as second-line therapies in recent years, splenectomy is still the better choice with less cost and more efficiency. Laparoscopic splenectomy (LS) for ITP proves to be a safe technique associated with lower morbidity and faster recovery and similar hematological response when compared to traditional open splenectomy. Based on the unified hematological outcome criteria by current international consensus, the response rate of splenectomy should be reassessed. So far, there are not widely accepted preoperative clinical indicators predicting favorable response to LS. Since the patients undergoing surgery take the risk of complications and poor hematological outcome, the great challenge facing the doctors is to identify a reliable biomarker for predicting long-term outcome of splenectomy which can help make the decision of operation.

Key words: Laparoscopic splenectomy; Corticosteroids; Open splenectomy; Hematological outcome; Predictor; Biomarker; Immune thrombocytopenia

Core tip: Despite the new drugs developed to treat primary immune thrombocytopenia, splenectomy is still

the main therapy for patients who fail corticosteroid treatment. Laparoscopic splenectomy proves to be a preferable technique compared to open splenectomy. The response rate to splenectomy should be reassessed based on the unified outcome criteria by current international consensus. So far, there are not widely accepted preoperative indicators predicting response to laparoscopic splenectomy. The challenge facing the doctors is to identify a reliable predictor of long-term outcome of splenectomy which can help make the decision of operation.

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INTRODUCTION

Primary immune thrombocytopenia (ITP), formerly known as idiopathic thrombocytopenic purpura or primary immune thrombocytopenic purpura, is an immune-mediated disease characterized by bleeding complications and low platelet counts in both children and adults[1]. ITP occurs at an annual rate of 1.9 to 6.4 per 100000 children and 3.3 per 100000 adults[2]. Bleeding symptoms are highly variable in primary ITP. According to a newly published systematic review that enrolled all prospective ITP studies with 20 or more patients, weighted proportion for intracerebral hemorrhage (ICH) was 0.4% for children and 1.4% for adults, and severe (non-ICH) bleeding rate was 20.2% for children and 9.6% for adults[3]. The term "purpura" was inappropriate because bleeding symptoms are absent or minimal in a large proportion of cases[4,5]. Therefore, an International Working Group (IWG) of recognized experts suggested to replace the original term "idiopathic thrombocytopenic purpura" or "immune thrombocytopenic purpura" with the term "immune thrombocytopenia"[1]. The new term was soonly accepted by the American Society of Hematology (ASH) and the new ASH guidelines[6].

Corticosteroids were introduced in the 1950s to treat ITP[7]. Until now, corticosteroids are still recommended as the first-line therapy in primary ITP by current international consensus[8]. However, only 20%-40% of patients can achieve a stable response with steroid treatment[9,10]. Splenectomy is recommended as the main second-line method for patients who do not respond to steroid or relapse for a long time[1]. Since the first laparoscopic splenectomy (LS) was reported by Delaitre *et al*[11] in 1991, this technique has gradually replaced traditional open splenectomy (OS) in surgical treatment of ITP. The following is our review of the current status and challenges of LS for ITP.

OVERVIEW OF PATHOPHYSIOLOGY OF ITP

Understanding of the immunopathogenesis of ITP is very important for treatment of this disease. The mechanisms which cause the accelerated platelet destruction and the inhibited platelet production are very complicated and intricate, for several abnormalities are involved in its immunopathogenesis. In terms of humoral immune dysregulation, the increased expression of B cell-activated factor and cyclophilin ligand interactor can prolong the survival and enhance the proliferation of B cells[12], and B cells can produce substantial antiplatelet autoantibodies against GP Ⅱb/Ⅲa and GP Ⅰb/Ⅸ[13]. Macrophages in the spleen and liver can destroy those autoantibody-combined platelets, causing the accelerated platelet destruction. Besides that, autoantibodies can also inhibit megakaryocyte production and maturation and platelet release, thus leading to the decreased platelet production[14]. As for cellular immune dysregulation, multiple cell types are involved in the development of ITP. $CD4^+CD25^+$ regulatory T cells (Treg cells) which can depress T cell responses are found quantitatively and functionally impaired[15]. In patients with ITP, the considerably high Th1/Th2 ratio[16], the increase of Th17 and Th22 cells[17], and the augment of $CD3^+$ cytotoxic T cells have been found[18]. Dysfunctions of macrophages and dendritic cells also take part in the immune disequilibrium of ITP patients[19].

THE STATUS OF SPLENECTOMY IN THE ERA OF NEW SECOND-LINE THERAPIES

Both intravenous anti-D immunoglobulin (IV anti-D) and intravenous immunoglobulin (IVIg) are recommended as first-line therapies for ITP in the international consensus report of IWG[1]. Either IV anti-D or IVIg produces short-term responses within 24-48 h in 60%-80% of patients. However, the responses are rarely durable beyond 4 wk[20,21]. In the past few decades, splenectomy is considered the first choice for ITP after failure treatment of corticosteroids. In recent years, some new drugs are developed to treat ITP and recommended as second-line therapies. These drugs include the monoclonal anti-CD20 antibody rituximab, recombinant human thrombopoietin molecule (rhTPO), and thrombopoietin receptor agonists (TPO-RAs). Some promising results have been reported in the treatment of ITP with these drugs. Thus whether continuing to regard splenectomy as the main second-line therapy has evoked much controversy. Rituximab has a depleting effect on B lymphocytes. However, its long-term effect is modest, for no significant differences in treatment failure rate within 78 wk between rituximab and placebo had been found [32 (58%) of 55 *vs* 37 (69%) of 54][22]. RhTPO and TPO-RAs (Eltrombopag and Romiplostim) can considerably promote the platelet production, but ITP patients should rely on these medica-

Table 1 Case series reporting 50 or more patients undergoing splenectomy for immune thrombocytopenia that contain platelet count response

Publication date	Accrual years	Ref.	Country	No. patients	Operation method	CR rate	R rate	NR rate	Relapse
2006[1]	1993-2003	Balagué *et al*[34]	Spain	103	LS	NA	NA	4.9%	6.1%
2007[2]	1988-2006	Sampath *et al*[29]	Canada	105	LS, OS	NA	NA	NA	21.6%
2007[1]	1994-2004	Kang *et al*[35]	South Korea	59	LS	47.5%	40.7%	11.9%	15.2%
2011[3]	2005-2010	Chen *et al*[36]	China	81	LS	88.9%	8.6%	2.5%	NA
2011[4]	1999-2006	Zheng *et al*[37]	China	127	LS	79.5%	9.5%	11%	9.7%
2013[3]	1982-2011	Gonzalez-Porras *et al*[38]	Spain	218	LS, OS	80.7%	8.3%	11.0%	36.1%
2014[3]	1995-2012	Montalvo *et al*[39]	Mexico	150	LS	88.7%	2.7%	8.6%	NA
2014[3]	2001-2009	Rijcken *et al*[40]	Germany	72	LS	77.8%	9.7%	12.5%	30.2%
2014[3]	2010-2012	Cai *et al*[41]	China	88	LS	77.3%	19.3%	3.4%	NA
2015[3]	1992-2013	Navez *et al*[42]	Belgium	82	LS	72.0%	24.4%	3.6%	NA

[1]Remission was defined as CR when platelet count increased to > 150 × 10^9/L, and as R when it was 50-150 × 10^9/L; [2]The criterion of ITP remission was not mentioned in the study; [3]Remission was defined as CR when platelet count increased to > 100 × 10^9/L, and as R when it was 30-100 × 10^9/L; [4]Remission was defined as CR when platelet count increased to > 100 × 10^9/L, and as R when it was 50-100 × 10^9/L. OS: Open splenectomy; LS: Laparoscopic splenectomy; CR: Complete response; R: Response; NR: No response; ITP: Immune thrombocytopenia.

tions, since these drugs only have short-term therapeutic effects[6,23]. Eltrombopag and Romiplostim were approved by the Food and Drug Administration for clinical use. While in many countries, these two drugs are unavailable. Splenectomy is also the second-line therapy for ITP patients who do not respond to first-line therapy. About 80% of ITP patients respond to splectomy and about two-thirds achieve a lasting response with no additional therapy for at least 5 years[8]. A systematic review of 23 articles and 1223 patients showed that by the resection of the site of platelet destruction and antiplatelet antibody production, laparoscopic splenectomy can cure 72% of ITP patients with long-term response[24]. Compared with expensive therapies with these drugs, splenectomy is less costly and more efficient[25]. Therefore, splenectomy is the better choice of the second-line therapy for ITP patients, especially in the developing countries.

TECHNIQUE ASPECTS OF LS

The comparison of the long-term outcomes and safety between LS and OS is always an issue. One systematic review[26] published in 2004 and some case series[27-29] in the past decade suggested that the hematologic efficacy of LS is the same as that of OS, while LS had fewer complications and mortality than OS. The systematic review[26] including 47 case series reported that mortality was 1.0% with OS and 0.2% with LS. Complication rates were 12.9% with OS and 9.6% with LS. The common complications of splenectomy include bleeding, thrombosis, pancreatic leakage, infection, prolonged hospitalization, requirement for additional intervention and readmission to the hospital; however, all the studies were retrospective. Randomized studies are needed to confirm this conclusion. LS has other advantages such as less postoperative pain, shorter hospital stays and better cosmetic outcomes[27,30]. Therefore, LS is preferred over OS for ITP by more and more surgeons.

In recent years, there are some case reports about the application of single-incision LS[31-33]. This technique emphasizes the concept of operation through one small transabdominal incision rather than the traditional multiple trocar sites, in order to show benefits of less pain and better cosmetics. However, because of the limited number of included patients in these studies, no obvious advantages of this technique could be showed when compared with traditional LS[31].

HEMATOLOGICAL OUTCOME CRITERIA

The response rate to splenectomy for ITP in different studies differs from each other. Case series[29,34-42] reporting 50 or more patients undergoing splenectomy for ITP that contain platelet count response are listed in Table 1. All these data were published in recent ten years and searched from PubMed database. One of the main reason for the discrepancies of hematological outcomes is the different definitions and clinical criteria which were used in different studies[9,43,44]. Fortunately, the standard terminology, definitions and outcome criteria for ITP have been unified[1,6]. In the new guidelines updated by ASH[6], a platelet count < 100 × 10^9/L was diagnosed as thrombocytopenia and a platelet count > 100 × 10^9/L or 30 × 10^9/L was diagnosed as complete response or partial response after splenectomy. The recommendations for using 100 × 10^9/L as an upper-threshold were based on three reasons: Over 10 years of follow-up, only 6.9% of patients with a platelet count between 100 and 150 × 10^9/L may develop a persistent platelet count < 100 × 10^9/L[45]. In some non-Western healthy individuals, platelet count values may be between 100 and 150 × 10^9/L[46-48]. Using 100 × 10^9/L as a threshold would reduce inclusion of most women with pregnancy-related thrombocytopenia[49]. The new guidelines will provide the evidence-based guidance for the diagnosis and therapy of ITP, as well as unified criteria for evaluating treatment outcome.

PREDICTORS OF SPLENECTOMY

Splenectomy is benefit for most of the patients, but there are still some patients who have a poor long-term

response. They should also take the risk of surgery, in the worst case, even death. So the choice of surgery is a deliberate decision. Many studies have attempted to determine reliable predictors of hematological response to splenectomy. Some factors including younger age[50,51], preoperative platelet count after using steroids and immunoglobulins[40,42], response to preoperative steroids[52,53], shorter disease duration (from diagnosis to splenectomy)[51], and splenic sequestration[54,55] have been reported as successful predictors of splectomy for ITP. But all the above conclusions cannot be verified in other studies. So far, there have been not widely accepted preoperative clinical indicators predicting response to splenectomy. Identifying a preoperative biological or immunological marker to predict long-term results of LS for patients with primary ITP will be the focus of future research. Our team has made preliminary progress toward this goal[56]. In our study, we showed that preoperative heptoglobin in serum may be a favourable predictor for the long-term response to splenectomy in ITP. Further studies with long-term follow-up and larger sample size are needed to confirm this finding. With the efforts of hematologists and surgeons, identifying biomarkers for favorable hematological outcome of ITP patients undergoing splenectomy and therefore avoiding invalid operation may come true in the future.

In summary, although some new drugs are developed as second-line therapies for primary ITP, splenectomy is still recommended as the first choice for patients who fail corticosteroid therapy. LS is a good alternative to OS for treatment of ITP. The great challenge facing the doctors is to identify a reliable predictor of long-term outcome of splenectomy which can help make the decision of operation.

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