

Long-term Follow-up of Laparoscopic Splenectomy in Patients with Immune Thrombocytopenic Purpura

Laparoscopic splenectomy (LS) has been reserved for intractable and relapsing immune thrombocytopenic purpura (ITP) despite medical treatment. With further experiences of LS in ITP, we investigated long term outcomes of LS, especially newly developed morbidities, and tried to find predictive factors for favorable outcomes. From August 1994 to December 2004, fifty-nine patients whose follow-up period was more than 12 months after LS were investigated. After a long-term follow-up (median 54 months, range 12.5-129 months), a complete response (CR) was found in 28 patients (47.5%), partial response in 24 (40.7%), and no response in 7 (11.9%). The relapse rate during follow-up periods was 15.2%. The rapid response group ($p=0.017$), in which the platelet count increased more than twice of the preoperative platelet count within 7 days after LS, relapsing after medical treatment ($p=0.02$), and the satisfactory group as the initial result of LS ($p=0.001$) were significant for predicting CR in univariate analysis, but only the initial satisfactory group was an independent predictive factor for CR in multivariate analysis ($p=0.036$, relative risk=6419; 95% CI, 1.171-35.190). Infections were the most frequent morbidities during the follow-up period, which were treated well without mortality. LS is a safe and effective treatment modality for ITP. Active referral to surgery might be required, considering complications and treatment results related to long-term use of steroid-based medications.

Key Words : *Laparoscopic Splenectomy (LS); Immune Thrombocytopenic Purpura (ITP); Follow-up*

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INTRODUCTION

Since Kaznelson suggested the possibility of splenectomy as a treatment for immune thrombocytopenic purpura (ITP), laparoscopic splenectomy (LS) has been an important treatment for ITP with the introduction of laparoscopic techniques for splenectomy (1, 2).

In ITP, it has been known that the spleen plays a central role in the pathophysiologic process. The spleen is not only the place to produce auto-antibodies for self platelets, but also the site where the platelet-antibody complexes are destroyed. The medical therapy based on steroids is the first choice of treatment, and surgical intervention, splenectomy, is reserved for the cases of refractoriness for medical treatment, dependence on steroids, and complications from medical treatment.

ITP accounts for more than 60% of the total indication for LS (3-6), and the response rate for LS has been reported from 50% to 80% (1, 7, 8). However, in general, follow-up periods after LS has not been long enough and operative complications were limited to perioperative complications and overwhelming postsplenectomy infection (OPSI), which give

just limited information about long-term outcomes after LS for ITP (1-4, 7, 8).

We have already reported early experiences of LS in patients with ITP (8) and the long-term results, of which the number of total patients was 40 and the mean follow-up duration was 29 months (2). With further experiences of LS in ITP, we investigated long-term outcomes of LS, newly developed morbidities, and predictive factors for favorable outcomes comparing the data to previous studies (2, 8).

MATERIALS AND METHODS

We reviewed the available medical records of 88 patients with ITP who underwent LS from August 1994 to December 2004 in Yonsei Medical Center, Seoul, Korea. Among them, available medical records of 59 patients whose follow-up period was more than 1 yr were investigated. We described the results of LS into the categories of early results and late results (2, 8), and we followed up patients based on out-patients' medical records and standardized personal question-

naires conducted by personal telephone when medical records were not available.

Defining treatment results of LS and predictable factors

Early results of LS were classified as in the following manner. We defined patients as the satisfactory group (S) when their platelet count after LS was more than 150,000/ μ L with a tapering dose of steroid or without medication on discharge. To the contrary, patients whose platelet count was less than 150,000/ μ L or without a tapering dose of medication on discharge were defined as the unsatisfactory group (US).

We categorized follow-up results according to this criteria: 1) during the long term follow-up, if the patient's platelet count after LS was over 150,000/ μ L with neither medication nor bleeding symptoms for more than 2 months, then we considered the patients as showing complete response (CR); 2) partial response (PR) was the term used where LS resulted in patients' platelet counts over 50,000/ μ L with a smaller dose of steroid than preoperative; 3) no response (NR) was used to describe patients in whom LS resulted in no response or a platelet count increasing to less than 50,000/ μ L with the therapeutic dose of medication; 4) we regarded patients as relapsing when, among the patients in the early satisfactory group, patients' platelet count became less than 100,000/ μ L and resumed medical treatment during follow-up.

To facilitate the statistical analysis of the data, we also made other variables as follows: 1) rapid response group, patients whose postoperative platelet count increased more than twice of preoperative platelet counts within the 7th postoperative day, 2) slow response group, patients who did not belong to the category of the rapid response group. We also categorized our data based on clinical characteristics and investigated the predicting factors for CR.

Data analysis

Statistic analysis was carried out with SPSS, version 10.0.

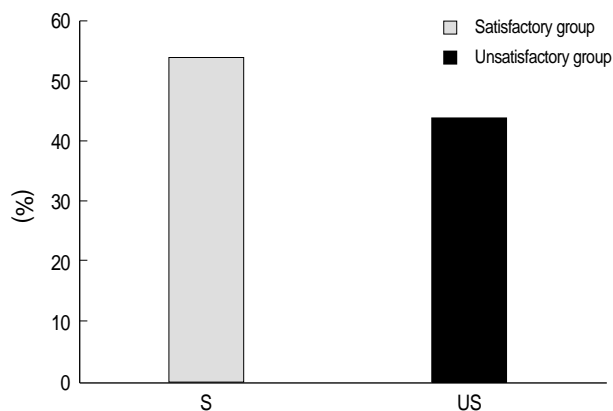


Fig. 1. Early results of laparoscopic splenectomy in immune thrombocytopenic purpura.

Differences were evaluated by the chi-square test and Student's t-test. A *p* value less than 0.05 was considered as statistically significant. The variables found to be significantly related to favorable outcomes (complete remission) were subsequently evaluated with multiple logistic regression analysis.

RESULTS

General characteristics

The median age of the patients (51 women and 8 men) was 32 yr (range, 18-70 yr). Thirty-one (52.5%) patients had associated diseases. Metabolic disease, including diabetes, was the most common among them, and systemic lupus erythematosus (SLE) was combined with ITP in 3 patients. Six patients had previous abdominal surgery, 4 had appendectomies, and 2 had salphingo-oohoprectomy. The median platelet count at the time of diagnosis of ITP was 36,000/ μ L (range, 30,000-99,000/ μ L). Thirty-one (55.4%) patients took only steroids as medical treatment, and 25 patients (44.6%) received a combined medical regimen, including danazole, vincristine, cyclosporine. With regard to the indication of LS, medical refractoriness were found in 31 patients (55.4%), relapsing during the course of tapering medication in 26 (medical relapsing, 46.4%), and complications of medical treatment such as weight gain, general weakness, acne, cushing appearance in 23 (medical complication, 41.1%). Median follow-up periods in the Department of Medicine before surgery was 7 months (range, 0.5-74 months).

Operative results

The median operation time was 125 min (range, 65-250 min). Accessory spleens were found in 8 patients (13.6%). Among them, 2 patients were found to have accessory spleens on the spleen scan done for evaluation of relapse after LS, which were all excised by reoperation. Three cases (5.1%) had to be

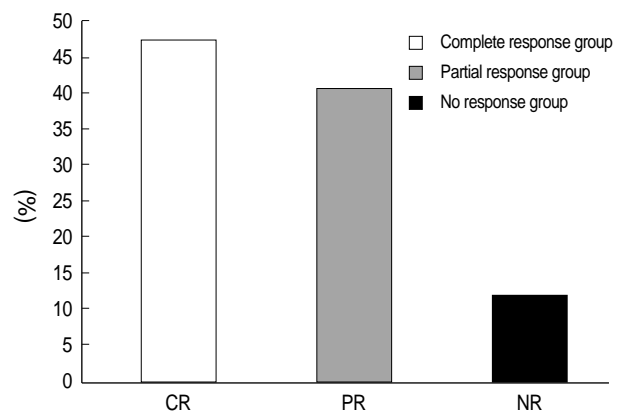


Fig. 2. Follow-up results of laparoscopic splenectomy in immune thrombocytopenic purpura.

Table 1. Determination of predicting factors for complete remission

	Complete response		<i>p</i> -value
	No	Yes	
Gender			
Male	7	3	4
Female	44	22	22
Age (yr)	39.2±12.4	36.1±13.4	NS
Pregnancy			
No	42	18	24
Yes	9	7	2
Incidental diagnosis			
No	19	16	8
Yes	31	14	17
Medical refractoriness			
No	22	10	14
Yes	24	14	10
Medical relapsing			
No	22	15	7
Yes	26	9	17
Medical complication			
No	27	12	15
Yes	21	12	9
Rapid response group			
No	25	16	9
Yes	21	6	15
Early result			
US	24	18	6
S	26	7	19
Preop. IVIG			
No	19	9	10
Yes	23	12	11
Accessory spleen			
No	40	20	20
Yes	5	2	3
Spleen weight (g)	126.2±64.3	121.6±45.1	
Medical follow-up (month)	15.6±18.4	18.1±22.1	NS
PLT at diagnosis. ($\times 10^3/\mu\text{L}$)	39.2±25.7	29.3±25.5	NS
Preoperative PLT ($\times 10^3/\mu\text{L}$)	74.1±57.8	11.2±75.9	NS
Medical regimen			
Steroid only	31	25	6
Steroid+others	25	22	3
Preop. PLT transfusion			
No	18	9	9
Yes	27	13	14

IVIG, intravenous immunoglobulin; PLT, platelet count; NS, not significant.

converted to open splenectomy. Two cases of conversion were caused by uncontrolled bleeding during the dissection of the splenic hilum, the other one was by the loss of spleen in the delivery process of the specimen. The median spleen weight was 135 g (range, 37-260 g), and postoperative drain was used in 40 patients (78.1%). Patients' oral intake began on median postoperative d2 after LS (range, 0-6 days). Complications related to LS were found in 6 patients (10.9%) and 7 complications were observed. Postoperative bleeding was found in 2, patients, abdominal abscess in 2, wound infection in 2

Table 2. Logistic multivariable regression analysis

Variables	Exp (B)	95% confidence interval	<i>p</i> -value
Medical relapsing	3.968	0.939-16.758	0.061
Early result	6.419	1.171-35.190	0.032
Rapid response	1.576	0.287-8.650	0.601

Table 3. Newly developed health problems after laparoscopic splenectomy

	Frequency
Avascular necrosis (femur neck)	5
Intestinal obstruction	1
Thromboembolism	1
Osteoporosis	2
Neurologic symptoms	4
Tumor	5
Infection	10
SLE	1

SLE, systemic lupus erythematosus.

and electric burn injury to the small bowel leading to segmental resection in 1 patient.

Early and late results of LS

Early results of LS showed that 32 patients (54.2%) were in the satisfactory group (S) and 26 patients (44.1%) in unsatisfactory group (US) (Fig. 1).

Among 88 patients, 59 patients were followed up for more than one year (median 54 months; range, 12.5-129 months; follow-up rate, 67.5%). With regard to late results of LS, 28 patients (47.5%) were categorized as CR, 24 patients (40.7%) as PR, and 7 patients (11.9%) as NR (Fig. 2).

Nine (15.2%) patients, among patients in early satisfactory group, had relapsed during the follow-up period. When looking into the pattern of relapsing, single relapsing was found in 6 (66.6%) patients and relapsing more than twice in 3 (33.3%).

Determination of prognostic factors for complete remission

The clinical and laboratory variables were examined by univariate analysis (chi-square) in relation to the achievement of CR after long-term follow-up. Three variables were found to have a prognostic value for CR in univariate analysis (Table 1). The rapid response group ($p=0.017$), in which the platelet count increased more than twice of the preoperative platelet count within 7 days after LS, relapsing after medical treatment in preoperative setting (medical relapsing, $p=0.02$), and the satisfactory group as an initial result of LS ($p=0.001$) were statistically significant in predicting CR after LS. These individually significant prognostic variables were subsequently included in multiple logistic regression analysis, which re-

vealed that only the initial satisfactory group ($p=0.036$, relative risk=6.419; 95% CI, 1.171-35.190) after LS was an independent prognostic factor for CR (Table 2).

Newly developed health problems during follow-up

During the follow-up period after LS, infection was the most common newly developed problem (Table 3). This included 5 cases of pneumonia, 2 cases of viral infection, such as herpes zoster and human poliovirus, 1 case of fungal sinusitis, 1 case of aseptic meningitis, and 1 case of tuberculosis pleurisy. Avascular necrosis of the head of femur, peripheral neuropathy, SLE, pulmonary thromboembolism, benign masses in the thyroid, breast, and ovary were also noted.

DISCUSSION

Previous reports on long-term results of LS in ITP had somewhat limited follow-up periods, making it difficult to exactly define the long-term outcome of LS for ITP (2, 3, 7, 8). According to our data, the early result of LS reveals that 54.2% of patients belonged to the satisfactory group, and the late follow-up results showed that CR was 47.5%, PR was 40.7%, and NR was 11.9%. These results of CR were dependent upon the criteria of patients' platelet count (more than 150,000/ μ L), clinical symptoms, and the status of medical treatment. However, from the clinical point of view, many heterogeneous patients compose the PR group according to these criteria. In other words, some patients with their platelet counts between 100,000/ μ L and 150,000/ μ L without medical treatment and no bleeding symptoms belonged to the PR group where most patients with their platelet counts more than 50,000/ μ L with medical treatment and bleeding symptoms. Considering these weak points of the criteria used in this study, the clinical results of LS in ITP can be re-estimated as follows: when we define 100,000/ μ L as the point for favorable outcome, 42 patients (72.4%) belonged to the satisfactory group and 16 (27.6%) to the unsatisfactory group; likewise, CR was 66.1% (39 patients), PR was 22% (13 patients), and NR was 11.9% (7).

Other researchers suggested that age, response to preoperative medical treatment, the period from the diagnosis of ITP to splenectomy, and the degree of platelet response after splenectomy are known as predictive factors for favorable outcomes of splenectomy in ITP. Our previous study (2) on this issue revealed that the rapid response group had a predictive value in univariate analysis, whose platelet counts after LS increased more than twice within a week. This rapid response group also had a significant value for predicting favorable outcomes (CR) in this study. Therefore, a current follow-up study could confirm the meaning of the rapid response group for predicting favorable long-term results after LS in ITP.

In the current study, one of the indications of splenectomy

in ITP, that is, relapsing cases ("medical relapsing") during the tapering of medication, was another predictive value in univariate analysis ($p=0.02$, Table 1). Multiple regression analysis showed that medical relapsing can predict favorable outcomes after LS and its relative risk was about 4 times (Exp (B)=3.968, p -value=0.061, 95% CI: 0.939-16.758). Even though the p -value was not less than 0.05, we expect this value could be significant if enough patients' data were collected. Long-term medical treatment can make the patients exhausted and reduce the quality of life. Taking the fact that the patients' population was mostly female and also the side-effects of long-term medical treatment into consideration, this result suggests that patients with relapses after medical treatment need to be referred to the Department of Surgery for LS without further medical treatment. Recent observation performed by Kwon et al. (9) supports this suggestion. Based on 30 LS on patients with ITP, they concluded that splenectomy for steroid nonresponders resulted in inferior response rates as compared with those who experienced relapse after steroid treatment (55.6% vs. 91.7%, $p=0.042$), and the time between diagnosis and surgery is another predictive factor for favorable outcomes ($p=0.049$).

Another predictive factor for favorable outcome is the early result of LS. The satisfactory group is the most potent and independent predictive factor in our study (Exp (B)=6.419, $p=0.032$, 95% CI: 1.171-35.190). In fact, 9 patients (15.2%) had relapsed with their platelet count less than 100,000/ μ L and took medications again, which is not very different from other reports (7, 10). Most patients with cases of relapse took steroids combined with various doses of danazole, vincristine, immuran, and cyclosporine. On the other hand, the rest (84.8% patients in the satisfactory group) could be categorized into CR without any relapsing or any additional medications. This result can address the notion that early satisfactory response after LS in ITP can be sustained for a prolonged time without relapsing, which means that LS is a very effective treatment modality in ITP.

Accessory spleen has been regarded as an important factor causing relapsing when not adequately removed in LS (11). However, current results showed only two relapsing patients revealed to have accessory spleen. After excising all accessory spleen, both patients belonged to PR. This result could not explain the accessory spleen itself and is only responsible for relapsing after splenectomy. Considering other articles showing that only 25-75% of patients had good results after the excise of accessory spleen (5, 12), our result suggests that other possible mechanisms might be related to the recurrence after LS, such as sequestration of platelets in marrow or liver, not to mention the accessory spleen itself (13).

With respect to newly developed health problems observed during follow-up periods, infectious diseases were most commonly discovered in 10 patients. The overall incidence of septicemia is low in adults, but death rates from OPSI have been reported to be up to 600 times greater than in the gen-

eral population, with a lifetime risk for OPSI of 5% (14). Though almost all patients did not receive a preoperative vaccination in our study, fatal infectious disease was, fortunately, not found. However, pneumonia occurred in 5 patients, who were admitted to hospital to receive proper management. We consider that much efforts should be made for safe LS and the prevention of OPSI. So, we have recently started a preoperative vaccination against pneumococcus and *H. influenza* prior to splenectomy. In addition, we recommend that those patients who underwent LS get vaccinated for influenza annually based on the clinical experiences that the patients who underwent LS seem to often contract common colds. The common cold might play roles in triggering secondary pulmonary bacterial infection. We believe the education of patients over the status of patients' immunity is important. They should be informed of the necessity for follow-up especially when their infectious symptoms are not alleviated for a long time and become even more aggravating. These strategies are compatible with the 2001 guidelines for preventing OPSI (15). On the issue of prophylactic antibiotics to prevent OPSI, however, we do not have confidence in this policy since patients' compliance, the uncertain efficacy of prophylactic antibiotics, and the emergence of antibiotics resistance bacteria, should be considered.

An increased incidence of atherosclerotic events, such as cerebrovascular accident and heart disease, have been reported after splenectomy because abnormal erythrocytes may remain longer in the circulatory system, initiating platelet activation, as well as thrombocytosis after splenectomy (1). In our data, just one patient experienced pulmonary thromboembolism. This patient had SLE at the time of the diagnosis of ITP. However, this case was concluded to be related to antiphospholipid syndrome in SLE patients based on laboratory and patients' history as reported in other articles (16).

Avascular necrosis of the femur head and peripheral neuropathy are believed to be related to long-term use of medications prior to LS, such as steroid and vincristine. Hence we would like to recommend LS as early as possible in patients with ITP in order to reduce the complications related to long-term use of medication. Especially with the advancement of laparoscopic skill and experiences, we recently have been performing LS with a three-port method, and with a very low rate of complications. According to our data, the median operative time was 77.5 min (range, 60-115 min), and the median length of hospital stay has been 4 days after surgery (range, 2-11 days) since 2001.

In summary, we are sure that LS is a very effective and safe treatment for ITP based on our long-term follow-up results. The initial satisfactory group after LS is a potent independent predictive factor for favorable outcomes. Long-term follow-up is necessary because of not only relapsing but also newly developed health problems after LS such as infection and other clinically important issues.

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