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Prognostic factors for positive immune thrombocytopenic purpura outcome after laparoscopic splenectomy

Research Article

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Abstract: Laparoscopic splenectomy is considered as a second step treatment for ITP patients. The purpose of this study was to determine efficiency of laparoscopic splenectomy for ITP patients and to identify the independent prognostic factors that may predict the positive outcome. Two hundred and thirty nine patient medical records were analyzed retrospectively. The special questionnaire, which included present platelet count, the steroid usage and its dosage, was sent to all patients. The complete response (CR) was defined, when the platelet count was above 130 x 109 /L. The 239 adult patients with a median age of 51.3 (16-93 years) were included in this cohort. The median follow up period was 75 months. 49 patients, who relapsed after steroid treatment, underwent laparoscopic splenectomy. The short term postoperative CR was 71.4% after laparoscopic splenectomy compared to 38.1% in non-splenectomized patients ($p < 0.000$). The long term CR was 79.5 % in patients after splenectomy compared to 47.4% in non-splenectomized patients ($p < 0.018$). After univaried analysis three clinical variables were found to be significantly related to splenectomy outcome: disease duration ($p<0.007$), preoperative platelet count ($p<0.049$) and platelet count on the third postoperative day ($p<0.000$). Multiple logistic regression analysis demonstrated, that only platelet count on the 3rd postoperative day > 129 x 109 /L ; RR=53.3 95% (CI, 1.888-1517.98) was significant predictor for long-term positive ITP outcome after laparoscopic splenectomy. Splenectomy is effective treatment for ITP. Platelet count > 129 x 109/L on the third postoperative day is the significant predictor of positive long-term outcome after laparoscopic splenectomy.

Keywords: *Licorice • Laparoscopic splenectomy • ITP • platelet count*

1. Introduction

ITP was first described by P. G. Werlhof in 1735 year, who called it “Morbus maculosus hemorrhagicus” [1]. ITP – is an autoimmune hematological disease, characterized by splenic production of antibodies against platelet glycoprotein complexes, resulting in a variable degree of thrombocytopenia. The spleen is not only the source of antiplatelet production, but also the predominant site of subsequent platelet sequestration and destruction [2]. Disease for adults often has a chronic course, which could last many years with recurrent relapses and requires frequent medical interventions [3]. ITP may be treated with one of several immune-modulating agents, with varying degree of success. The open splenectomy was the only standard treatment for ITP until the 1950s when steroids for treatment were introduced. The mainstay of medical therapy is bolus of steroids followed by a tapering dose. However, because few chronic ITP patients achieve complete remission with

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medical therapy, splenectomy is the main treatment. New laparoscopic approach for this idiopathic disease were introduced in 1991 [4,5]. Since 1991 laparoscopic splenectomy (LS) has overwhelmed the open operation, and laparoscopic intervention became the standard operation for ITP all over the world.

ITP is the most common indication for elective splenectomy [6], and the outcome is measured by the postsurgical platelet count. Many investigators have documented variables that may predict a successful response to splenectomy for ITP, which include younger age, successful response to preoperative steroids, a shorter interval from diagnosis to splenectomy, splenic sequestration, response to intravenous IgG, preoperative platelet counts. On the other hand, there exists some uncertainty: results of studies are controversial, different researchers show varying results, there aren't clear prognostic factor values [6-8]. The main task of surgeons remains to determine the factors that may predict a successful ITP outcome following LS.

The purpose of this study was to evaluate the efficiency of laparoscopic splenectomy for ITP patients and to identify the prognostic factors that may predict the positive outcome of this operation.

2. Material and Methods

We reviewed clinical medical history of 239 patients treated in the University Hospital from 1996 to 2006. The diagnosis of ITP was based on history, physical examination, complete blood count, bone marrow examination and exclusion of other potential causes of isolated thrombocytopenia.

All the patients received steroids (1 mg/kg per day) as initial treatment at the Clinic of Hematology. Indications for LS included: long-term treatment therapy refractory to steroids, intolerance of and yet dependence on medical therapy (prolonged use of steroids with side effect), need for critical steroid doses to achieve therapeutical effect, relapses during course of medical treatment and patient agreement to be operated. Response to treatment (laparoscopic or conservative) was evaluated according to platelet count: complete response (CR) when platelet count increased to > 130 x 10^9 /L; partial response (PR) when it was 50 – 130 x 10^9 /L or absent response (AR) when platelet count was < 50 x 10^9 /L. Short-term response was evaluated on the seventh day after treatment. Long-term follow-up evaluation was obtained from clinical records, the referring hematologist follow-up visits, phone interviews with both the patients and the referring hematologist within median 75 months after conservative or surgical

Figure 1. Patient's research scheme.

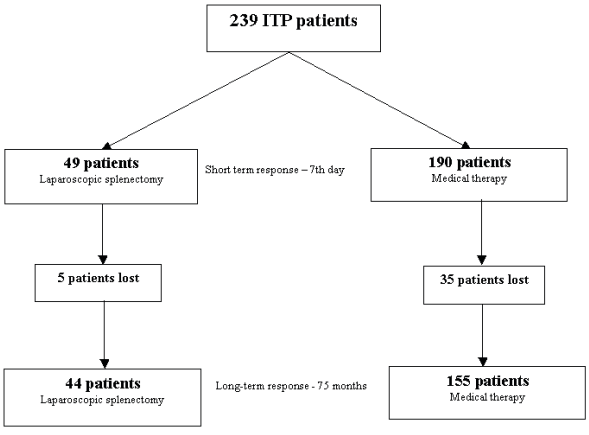
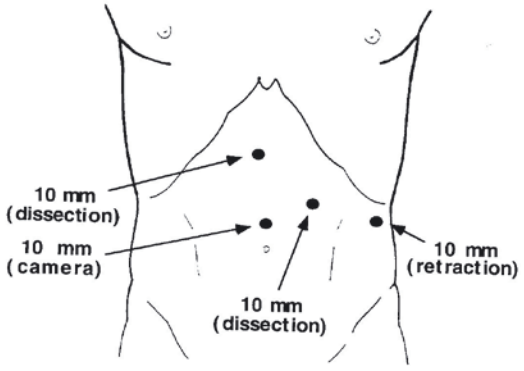


Figure 2. Troacar placement in LS.



treatment. Eight preoperative and postoperative values (disease duration, platelet count before surgery and on 3rd postoperative day, body mass index (BMI), age, gender, steroid treatment time, vincristin usage) were examined by univariate analysis and then subjected to multiple logistic regression analysis and likelihood ratio. Patient's research scheme is shown in Figure 1.

2.1. Principles of surgical technique in LS

- *Right semilateral supine position of patient with the left side up;*
- *Using five troacars (Figure 2);*
- *First dissecting splenic flexure away from the spleen;*
- *Dissecting splenophrenic and splenorenal attachments;*
- *Dissecting short gastric vessels with ultrasonic coagulating shears;*
- *Splenic hilar vessels individually controlling between clips, ligatures or endovascular staplers;*
- *Using a strong bag for spleen morcellation and specimen retrieval.*

Table 1. General patient characteristics.

Parameter	ALL ITP patients (n=239)
Age	51.3 (16 – 93)
Gender:	
male	28.5%
female	71.5%
Haemorrhagic syndrome	87.4%
Concominant diseases (respiratory, heart insuff. etc.)	30%

Table 2. Treatment efficiency.

Response characteristics	Operated patients	Medical therapy patients	p value
Short - term response (7th day):			
• CR	71.4%	38.1%	$p < 0.05$
• PR	10.2%	41.3%	$p < 0.05$
Long-term response (75 months):			
• CR	79.5%	47.4%	$p < 0.05$
• PR	-	36.8%	$p < 0.05$

2.2. Statistical analysis

The results are given as number of cases and percentage for categorical data and median (min – max) values for quantitative data. The relationship between the variables was evaluated initially by univariate analysis, contingency table, chi-square or Fisher's exact test for categorical data and t-test for quantitative data. Prognostic factors, related to long-term positive response to splenectomy, were determined using ROC curve, multiple logistic regression analysis and likelihood ratio. Data analysis was performed using SPSS software version 16 (SPSS, Chicago, IL, USA).

3. Results

General characteristics of patients are presented in Table 1.

Short-term and long-term response to medical and surgical (LS) therapy is shown in Table 2.

3.1. Response to splenectomy

Over a mean period of 75 months, 44 patients (89.8%) were available for follow-up. Five patients were lost. The CR rate was in 35 cases (79.5%). Nine patients (21.5%) did not respond to surgery (platelet count < 50 x 10^9 /L).

Accessory spleens were found in two patients (4%) before the LS from all 49 operated patients. We managed to remove these accessory spleens during laparoscopic splenectomies.

One patient (2%) had ITP relapse 2 weeks after laparoscopic splenectomy because of remained accessory spleen. We performed scintigraphy and CT scan and found this accessory spleen in the lodge of the removed main spleen. We performed relaparoscopy and this accessory spleen was successfully removed.

3.2. Univariate analysis

Patient's characteristics related to long-term response to laparoscopic splenectomy and results of univariate analysis are reported in Table 3. Within of 44 surgical patients, the three factors correlated with positive response in follow-up: the platelet count before surgery, disease duration and the platelet count on 3rd postoperative day.

3.3. Multivariate analysis

We used different statistical procedures for multivariate analysis of surgical patients. Using ROC analysis, cut-off prognostic values for three factors we reevaluated, obtained in univariate analysis: platelet count before operation - 59 x 10^9 /L (sensitivity 0.577, specificity 1-0.143); disease duration - 17 months (sensitivity 0.687, specificity 1-0.132) and platelet count on 3rd postoperative day - 129 x 10^9 /L (sensitivity 0.852, specificity 1-0.125).After this, multiple logistic regression analysis demonstrated that platelet count on 3rd postoperative day > 129 x 10^9 /L RR=53.3 (95% CI, 1.888-1517.98) was the only significant predictor for long-term positive ITP outcome after laparoscopic splenectomy.

Table 3. Patient characteristics related to long-term response to splenectomy (Results of univariate analysis).

Predictors	All operated patients (n=44)	Responders (n=35)	Nonresponders (n=9)	p value
Platelet count before operation	70 (1-260)	81.6 (6-260)	53.4 (1-241)	p<0.049
Platelet count on 3rd postoperative day	199 (1-453)	230 (29-453)	150.7 (1-405)	p<0.000
Disease duration till surgery (months)	40 (1-348)	17.1 (1-180)	71.6 (1-348)	p<0.007
BMI	27.8 (18-38)	29.7 (20-38)	26.5 (18-31)	p=0.6
Age	44 (16-81)	44.9 (20-75)	44.2 (16-81)	p=0.9
Male/female	1:1.5	1:1.8	1:2.3	p>0.05
Time of steroid treatment (months)	4.9	3.5	4.7	p>0.05
Vincristin usage (%)	12.4%	10.2%	12.2%	p>0.05

4. Discussion

There are many therapeutic regimens of initial ITP treatment. Different guidelines indicate steroids (prednisolone or dexamethasone) as the first step treatment for ITP patients. Despite their high initial response rate (50-90%), curative response is achieved only in 10-30% of patients [9-13]. Three studies analyzed the response rate of high-dose dexamethasone (30 - 40 mg/day orally for four days per month) as the first-step treatment. The short term response rate was 80 - 89% after a median follow-up of 31 months [14-16]. Documented studies indicate 50-65% of complete response after high dose of dexamethasone [10,17,18]. On the other hand, the most of patients relapse after stopping the steroid usage. Osteoporosis, hypercorticism, diabetes mellitus, infections are side effects due to prolonged steroid use [9-13]. Intravenous (IV) immunoglobulin (IG) can be used in combination with steroids or as monotherapy for ITP treatment. IG is the treatment of choice for patients who cannot tolerate steroids. For majority of patients IV IG increases platelet count more rapidly than steroids (short term response - 75 - 92%) [17-19].

The use of CD-20 antigen (monoclonal antibodies against B-cell) was analyzed in systematic metaanalysis which included more than 300 ITP patients [20-23]. The response rate was 25-75%, CR - 33% of cases, lasting up to three years [22-25] and the only common side-effect was infusion reactions [26]. Patel V. and colleagues documented ITP patients treated with monoclonal antibodies 5-year relapse-free and treatment-free survival of 72% and 61% respectively [27].

Thrombopoietin (TPO) receptor agonist's romiplostim and eltrombopag were recently approved for relapsed or refractory ITP treatment. In the controlled studies for ITP patients, romiplostim administration resulted in a durable platelet response defined at least for 61% of non splenectomised patients. The median time to peak platelet count was 10 days from the first dose [28,29]. Oral eltrombopag efficacy was 89% and 82% for splenectomized and non-splenectomized patients respectively with lasting effect for up to 2 years. However after discontinuation of TPO-mimetics a rapid decrease in the platelet count may occur [28,29].

Refractory ITP patients present as 25 - 30% of all ITP patients [9,17]. There are no evidence-based treatment guidelines for such patients [30]. The chances of inducing a durable and sustained remission are low [17]. Immunosuppressive and cytotoxic therapies are used less commonly, mainly to salvage severely affected and highly refractory patients [31]. Such therapies include vincristine, cyclophosphamide, azathioprine, danazol and newer agents such as cyclosporine A and mycophenolate mofetil are now often chosen.

Danazol, an attenuated androgen, with reduced virilizing effect compared with other androgens, has been successfully used for ITP patients: when patients were treated at least for 6 months, reported response rates have ranged in 10 - 80% of cases [32-34]. Responses may be durable, but around a half of cases requires indefinite maintenance of treatment [32,35]. The mechanism of danazol action would predict a high response rate to thrombopoietin TPO-mimetic agents [36].

Vincristine and vinblastin transiently increase the platelet count approximately in 70% of ITP patients within 5-21 days but produce sustained remissions only in 10 of treated patients [9,19,20]. Responding to treatment patients return to pretreatment platelet levels within days to weeks after cessation of therapy [14,19,37].

Cyclophosphamide reduces the number of T and B lymphocytes and suppresses their function. It increases platelet count in 85% of patients, with durable responses up to 50% after 2-3 months therapy [19,38]. Thrombocytopenia may worsen initially. Frequent adverse effects are neutropenia, infections, infertility, alopecia, secondary malignancy that limits the use of this drug for severe ITP cases [14,31].

Cyclosporine suppresses T-cell functions, inhibits

antigen-induced activation of CD4 + T lymphocytes and the production of interleukin-2 also other cytokines [39,40]. Response rates are seen in 50 - 55% of the patients, of which 30 - 40% has a CR [39,41]. The induced response can persist for several months and even years after treatment has been discontinued [31,39].

For the past 50 years, splenectomy has remained a standard treatment for adults with ITP who do not respond to steroid treatment or who continue to require steroids to sustain a safe platelet count [41,42]. K. Kojouri et al. systematically identified and reviewed 135 case series that described consecutive patients who had splenectomy for ITP [43]. They found, that relapses occurred in a median 15% of patients (range 0%-51%) with median follow-up of 33 months when case series reporting adults and children were analyzed. The relapse rate appeared to increase along with duration of follow-up, but the correlation did not reach statistical significance. Our study results demonstrate similar ITP relapse rate (20%) after laparoscopic splenectomy in adults with longer (75 months) median follow-up period.

ITP is the most common indication for splenectomy (50% - 80% of LS) [6]. Studies show, that almost 70% of ITP patients stop responding to conservative treatment and require splenectomy [44]. Most of the studies focus on short-term response to splenectomy, when defining long-term prognostic factors, however, different studies results wary in wide range [6,7,45].

Usually ITP remissions after LS occur in two years, but there have been cases when relapses occurred even in eighteen years after surgery. Considering this, long - term follow up is needed to evaluate the real efficiency of LS. Our study results demonstrate, that even 79.8% of all operated patients had long-term CR compared with 47.4% of medical treatment. An international expert panel in their consensus statement [6] also emphasized that LS is safe and highly effective in terms of complete and partial remission in patients with ITP. LS results are even superior to those for medical treatment due to high rates of complete remission in the absence of side effects related to medical therapy [6].

Among all of the prediction variables tested before splenectomy, younger age was found to be mostly associated with response [43,46,47]. Most studies demonstrate that age between 30 and 45 years is an independent prognostic determinant of a successful response to splenectomy [43,45,47-49]. On the other hand, approximately an equal number of studies demonstrated no correlation of age with response to splenectomy [43,50,51]. Furthermore, among the many studies that did demonstrate a correlation, there was no consistent age that distinguished responders from nonresponders [43]. We didn't find any significant differences in age between responders and nonresponders to LS in our study too.

Some studies demonstrate that duration of illness is a predictive factor of a successful response to splenectomy [52,53], but majority of others didn't find any correlation between these parameters in ITP patients [43]. Our study results demonstrate that cut-off prognostic factor value for disease duration could be approximately 17 months, but sensitivity 0,687 and specificity 1-0,143 are quite low, so this proposition needs further investigation and analysis.

Preoperative thrombocytopenia has been evaluated as a predictive factor for positive outcome by several studies [43]. Duperier T et al. in their study by multivariate analysis revealed that higher preoperative platelet levels were predictive of a successful response to LS regardless of how this level was achieved [47]. Furthermore, lower preoperative platelet levels were predictive of patients who would subsequently develop refractory ITP. In our study, univariate and ROC curve analysis identified platelet count before operation - 59 x 10^9 /L (sensitivity 0.577, specificity 1-0.143) as a cut-off prognostic factor value for successful response after LS. But multiple logistic regression analysis demonstrated, that only platelet count on third postoperative day > 129 x 109/L RR=53.3 95% (CI, 1.888-1517.98) is a significant factor for presupposing successful outcome after LS in adults. Another study assessed similar results as our study did. [50]. Kiarash Kjouri et al in their review [43] stated that among postoperative prediction variables, the magnitude and rate of the platelet count increase within the first 4 weeks after surgery were often, but inconsistently, reported to correlate with the response at 30 days following splenectomy. No summary statement about the relation of postoperative platelet count recovery to response is possible because the studies reporting predictive values used different criteria for platelet count levels and time after splenectomy [43].

The weakness of our study is that we could not find any significant preoperative predictors for successful ITP outcome after LS. The most useful predictive indicators in surgery are those, which can be assessed before surgery so that surgeons can counsel the patients whether the surgery is going to be of value or not. Although it is possible that some combination of preoperative characteristics may better predict the response to laparoscopic splenectomy, many patients without positive predictive characteristics also respond. On the other hand, considering the conflicting results among different studies, the research domain in this field is open, and further studies are warranted to establish independent predictive and prognostic factors for positive outcome after LS for ITP patients.

5. Conclusions

Our study demonstrates laparoscopic splenectomy to be an effective treatment for ITP in adults: short - term CR rate was 71.4%, long-term - in 79.5% of cases.

Multiple logistic regression analysis demonstrated that only platelet count on 3rd postoperative day > 129 x 10^9/L RR=53.3 95% (CI, 1.888-1517.98) is the significant predictor for long-term good outcome for ITP patients after laparoscopic splenectomy.

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