Role of Splenectomy in Chronic Idiopathic Thrombocytopenic Purpura

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Abstract

Aim of the study: To evaluate the usefulness of splenectomy and factors which predict long term remission in chronic idiopathic thrombocytopenic purpura (ITP).

Methods: We reviewed the data of 364 patients diagnosed as chronic ITP between January 1983 to December 1996 of whom 71 patients underwent splenectomy. The patients were followed up for an average period of 58 months and the short and long term response to splenectomy were analyzed at the end of one month and 60 months, respectively.

Results: At the end of one month after splenectomy, 82% had complete response, 7% partial response and 11% had no response. At the end of 60 months, 42% maintained complete response, 7% partial response, 34% had no response and 17% were lost to follow up.

The results were statistically evaluated by using non-parametric test (Chi-square test) to age, sex, platelet count prior to treatment, initial response to steroids, time interval between diagnosis and splenectomy and post-operative platelet count. Of these factors only preoperative response to steroids (p value = 0.018303) and postoperative platelet count (p value = 0.013536) were found to be significant, statistically to predict long term remission. Age, sex, initial platelet count and time interval between diagnosis and splenectomy didn’t seem to be statistically significant.

Conclusion: This study suggests, that patients with an initial complete response to steroids and a postoperative platelet count > 300 x 10^9/L at the time of discharge were associated with a long term remission. Splenectomy in ITP is a safe procedure with minimal morbidity and mortality and gives a good long term remission in steroid-failure patients with chronic ITP.

INTRODUCTION

Idiopathic thrombocytopenic purpura (ITP) is an acquired disease in adults and children characterized by a low platelet count, an essentially normal bone marrow and absence of evidence for secondary thrombocytopenia. In this, the antibody-sensitized platelets are destroyed prematurely in the reticuloendothelial system (RES). It can be acute or chronic, depending on the duration of the disorders. Traditionally, chronic ITP is defined as the persistence of thrombocytopenia for more than six months. Glucocorticoids and splenectomy have been the primary and most effective treatments of chronic ITP in adults. Glucocorticoids seem to increase the platelet production,1 diminish platelet sequestration and destruction of antibody sensitized platelets2,3 and this compliments the long term immunosuppressive effect of glucocorticoids. Glucocorticoids are also known to downregulate the expression of FcRn messenger RNA which prevents the catabolism of IgG.4,5 However complete long-term response was achieved only in about 30% of the patients.6,8 Splenectomy was first performed in 1916 for treatment of ITP9 even before glucocorticoid therapy was introduced. Now the current indication for this procedure is the failure to respond to glucocorticoids provided there are no contraindications for the procedure.10 Approximately 60% of the patients will achieve complete remission following splenectomy.5,8 The major effects seem to be due to the removal of major site of destruction of antibody sensitized platelets and the major site of antibody synthesis. In this study we have analyzed the short and long term responses to splenectomy in 71 patients and have tried to identify and focus on the possible prognostic factors that can predict the response to splenectomy.
**MATERIAL AND METHODS**

Between January 1983 to December 1996, 364 patients were diagnosed as chronic ITP at the Government General Hospital, Chennai, India of whom 71 patients underwent splenectomy.

The diagnosis of ITP was based on history, physical examination, complete blood count, peripheral smear and bone marrow aspiration. Following diagnostic criteria was used.

1. Platelet count lower than 30 x 10^9/L or 50 x 10^9/L with significant mucous membrane bleeding.
2. Normal or increased megakaryocytes in the bone marrow aspirate.

We did not do platelet associated IgG (PAIgG) assay. All patients underwent steroid therapy initially (Prednisolone 1 mg/kg body weight) and were considered for splenectomy due to failure of steroid therapy to reach or maintain adequate platelet count.

The following criteria were used to assess the response to treatment.

1. Complete Response (CR) - Platelet count > 150 x 10^9/L while maintained on no therapy for at least 2 months and continuing for the duration of observation of 60 months.
2. Partial Response (PR) - Increase of platelet count between 50-150 x 10^9/L.
3. No Response (NR) - Platelet count < 50 x 10^9/L.

The patients were followed up for a period ranging from 6 to 144 months after splenectomy (Average 58 months). The short and long term response to splenectomy at the end of 1 month and 60 months were analyzed.

Age at the time of diagnosis, sex, initial platelet count (pretreatment), initial response to steroids, duration between diagnosis and splenectomy and the platelet count after splenectomy at the time of discharge (approximately 15 days post-splenectomy) and the significance of these factors in assessing the response to splenectomy were done by using non-parametric test (Chi-square test) and the level of significance was a P value of < 0.01.

**RESULTS**

**Clinical Manifestations**

All the patients were symptomatic at the time of diagnosis. The commonest symptom being bleeding gums (70%), purpura/petechiae (61%), bleeding PV (30%), Epistaxis (14%). Major bleeding was an uncommon manifestation of ITP at the time of presentation among our patients, 7% had genitourinary bleed, 6% gastrointestinal bleed and 1% CNS bleed.

The male : female ratio was M:F - 1:6.1. The ages of the patients ranged from 5-55 years (Median - 34 years). Except one child aged 5 yrs., all were above 12 years as we are an adult hematology unit. The platelet count at the time of diagnosis ranged from 3-51 x 10^9/L (median = 20 x 10^9/L). The response to splenectomy is as shown in Table 1.

**Patient’s response to steroids and splenectomy**

Twenty one (30%) patient had no response to steroids, 33 (46%) patients showed partial response and 17 (24%) patients had an initial complete response and subsequently relapsed, while steroids were being tapered. The time interval from diagnosis and splenectomy varied between 1-92 months (average 10 months). Short and long term response to splenectomy were noted at the end of one month, and 60 months after splenectomy, respectively (Table 1).

Fifty eight (82%) patients had complete response, five (7%) patients had partial response and eight (11%) patients had no response to splenectomy at the end of one month. The followup period ranged from 6-144 months. The average duration of long term followup was 58 months. At the end of 60 months (5 years), 30 (42%) patients maintained complete response, 24 (34%) patients had no response, five (7%) patients partial response and 12 (17%) patients were lost to follow up.

<table>
<thead>
<tr>
<th>Table 1: Response to splenectomy</th>
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<tr>
<td>Immediate</td>
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<tr>
<td>N (%)</td>
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<tr>
<td><strong>NR</strong></td>
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<tr>
<td><strong>PR</strong></td>
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<tr>
<td><strong>CR</strong></td>
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Lost to follow up 17 (12%) NR · No Response; PR · Partial Response; CR · Complete Response

There was no post-operative mortality associated with splenectomy. During long term follow up, two patients developed pulmonary tuberculosis (one had reactivation of previous infection), five patients developed malaria (two had recurrent attacks of *Plasmodium vivax*), one patient developed sub-diaphragmatic abscess and recovered after treatment with antibiotics and one patient developed incisional hernia which was successfully repaired. None of the patients were immunized with pneumococcal and *H. influenzae* vaccine. Surgery was done without any platelet support or intravenous immunoglobulins (IVIg).

**Prognostic Factors**

Certain factors like the age at the time of diagnosis, sex, initial platelet count, initial response to steroids, time interval between the diagnosis and splenectomy and the post-operative platelet count at the time of discharge (2nd week) and their association with long term response were studied. The results have been related using a non-parametric test (Chi-square). Of these factors only preoperative response to steroids (P value = 0.018303) and post-operative platelet count (P value = 0.013536) were found to be significant statistically. Age, sex, initial platelet count and time interval between the diagnosis and splenectomy didn’t seem statistically related to splenectomy results (Table 2).
Table 2: Prognostic factors

<table>
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<th>Characteristics</th>
<th>Age</th>
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<tbody>
<tr>
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<td>0-30</td>
<td>31-60</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
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<tr>
<td>Age</td>
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<td>Platelet count at</td>
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<td>presentation x 10^9/L</td>
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<td>3</td>
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<td></td>
<td>Female</td>
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<td>Initial steroid response</td>
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<td>2</td>
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<tr>
<td></td>
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<td>10</td>
<td>4</td>
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<tr>
<td></td>
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<td>&lt; 6</td>
<td>19</td>
<td>6</td>
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<td>Increase in platelet</td>
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<tr>
<td>count post-operatively</td>
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<td></td>
<td>&gt; 300 x 10^9/L</td>
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<td>10</td>
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NR - No Response; PR - Partial Response; CR - Complete Response.

DISCUSSION

Chronic idiopathic thrombocytopenic purpura is an immune aberration in which antibody sensitized platelets are destroyed prematurely in the reticuloendothelial system, mainly in the spleen. Spleen plays a dual role by producing not only the antibody to platelets, but also destroying the antibody-coated platelets.

The treatment strategy has been aimed at reducing the antibody production, and destruction of these sensitized platelets by RE cells. These have been only successful in 2/3rd of patients suffering from this disease. We do not know the cause of antibody production to aim our therapy at the etiology. Remission recurrence and relapses occur as in any immunological disorder.

The first definitive therapy for ITP was splenectomy done in 1916. The discovery of steroids and its introduction in the treatment of this disorder, followed in 1950. Since then, steroids have been the primary modality of therapy in adults with chronic idiopathic thrombocytopenic purpura. Unfortunately only 1/3rd of patients have long term remission with steroids. For those patients, who require a high dose of steroids, more than 10 mg per day to maintain a minimum platelet count of 30 x 10^9/L or who have not responded to steroid therapy, splenectomy is recommended. Our policy has been to offer splenectomy also because of lack of compliance to long term therapy, difficulty in follow up of our patients, and the associated complications of long term steroid therapy, such as infection, hypertension, diabetes mellitus, steroid-induced osteoporosis and steroid-dependence. In taking this policy of splenectomy, we have taken to consideration the increased incidence of post-splenectomy sepsis and difficulty of vaccination against pneumococcus and Haemophilus influenzae infection and inability of our patients to afford intravenous immunoglobulin and platelet support because of cost.

We have done 71 splenectomies in steroid-failure patients with no operative mortality, without prophylactic vaccination, intravenous gammaglobulin and platelet support. Fifty-eight patients (82%) responded completely, immediately following surgery with 30 patients (42%) continuing to be in remission at 50 months post-operatively. Twelve patients (17%) have been excluded because of loss of follow up during 5 year follow up period of the study. We analyzed retrospectively these splenectomised patients for prognostic factors to predict long term remission.

Several studies have been done with varying conclusions. Some have suggested that those patients who responded to steroids will respond to splenectomy. The rationale for this has been, when antibody levels are low, the steroids will act better and splenectomy may permanently restore platelet-associated IgG to normal. However anti-platelet antibody can persist in plasma, in patients with ITP in clinical remission. In our study, the response to steroids has been found to be statistically significant in long term remission following splenectomy (p 0.018303) which was not found to be so in few studies in predicting splenectomy outcome.

Age and sex has been considered in few studies as a prognostic factor. Old patients above 60 years of age have a poor response to splenectomy. All our patients were fairly young (mean 23 years) therefore age was not a significant prognostic factor and so also the sex. The platelet count at presentation has also been of no significance prognostically. The post-splenectomy rise in platelet count > 300 x 10^9/L has been associated with long term remission in our study (P 0.013536). Early splenectomy, after the onset of the disease has been found to be a prognostic factor in few studies. This has not been so in our study. Patients who have had initial complete response to steroids therapy and a postoperative rise of platelet count > 300 x 10^9/L at one month, were associated with long term remission. Other non-surgical therapy to decrease the splenic function by splenic irradiation or splenic embolisation have been attempted with varying success.

The regrowth of spleniculi have been implicated as a cause of splenectomy failure. We have seen this only in one case so far. It has been our policy to ask our surgeon at splenectomy, to search the splenic bed and remove them. We have no facilities to search for them preoperatively by radionuclide scan.

Splenectomy carries a slight risk of predisposition to
infection by capsulated organisms in children. Vaccination with polyvalent pneumococcal vaccine, vaccine against *Haemophilus influenzae*, and quadrivalent meningococcal polysaccharide vaccine are advocated.\(^9\) In our study there was no infection by these organism, even though we have not immunized our patients against them. However, all patients except one were adults. We have had one case of subdiaphragmatic abscess which was treated with antibiotic therapy successfully. Prior exposure of our patients to these organisms due to our poor hygienic conditions in our country may have conferred some immunity.

Vaccination also does not confer full immunity. With no appreciable incidence of postoperative infectious complication, it may be prudent to reserve the vaccination to children requiring splenectomy in our country. Two patients had pulmonary tuberculosis and five patients had malaria and they were treated with appropriate therapy successfully. One patient developed incisional hernia which was successfully repaired.

Patients, who following splenectomy had platelet count < 50,000/\(\mu\)L or had bleeding problem were treated with steroids initially and those who did not respond were treated with various drugs like, cyclophosphamide (19 cases), vincristine (14 cases), colchicine (9 cases), vitamin C (7 cases), danazol (4 cases), and dapsone (1 case). Eight patients responded to cyclophosphamide, 4 patients to vincristine and one patient each to darazol and dapsone. Interferon, protein-A immuno adsorption, intravenous gammaglobulin, or plasmapharesis, were not used because of cost and non-availability in our setup.

Our study confirms the usefulness of splenectomy in chronic ITP in those who had failed to respond to steroids. Long term remission following splenectomy was seen in patients who had shown initial response to corticosteroids prior to splenectomy, or a significant increase in platelet count > 300 x 10^9/L immediately following splenectomy. Adults in our country may not need prophylactic vaccination against pneumococci or *Haemophilus influenzae*. Splenectomy is safe with no mortality even without platelet or intravenous gammaglobulin support.

**Acknowledgement**

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**REFERENCES**


