

HIGH-DOSE INTRAVENOUS IMMUNE GLOBULIN AND THE RESPONSE TO SPLENECTOMY IN PATIENTS WITH IDIOPATHIC THROMBOCYTOPENIC PURPURA

CALVIN LAW, M.D., MICHAEL MARCACCIO, M.D., PETER TAM, M.D., NANCY HEDDLE, M.Sc., AND JOHN G. KELTON, M.D.

ABSTRACT

Background High-dose intravenous immune globulin produces a temporary rise in the platelet count in patients with idiopathic thrombocytopenic purpura. Splenectomy may also be effective, but it is not possible to predict which patients will have a good response. We hypothesized that the response to intravenous immune globulin predicts the response to splenectomy.

Methods We studied retrospectively 30 patients with idiopathic thrombocytopenic purpura who had first been treated with immune globulin and then undergone splenectomy. The responses to the two treatments were classified on the basis of the platelet count as poor (<50,000 per cubic millimeter), good (50,000 to 150,000 per cubic millimeter), or excellent (>150,000 per cubic millimeter).

Results All nine patients who had poor responses to intravenous immune globulin also had poor responses to splenectomy at one year. Of the 21 patients with good or excellent responses to intravenous immune globulin, 19 had good or excellent responses to splenectomy.

Conclusions Patients with idiopathic thrombocytopenic purpura who have good or excellent responses to intravenous immune globulin are likely to have good or excellent responses to splenectomy, whereas patients who have poor responses to intravenous immune globulin are unlikely to have good or excellent responses to splenectomy. (N Engl J Med 1997;336:1494-8.)

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IDIOPATHIC thrombocytopenic purpura is a disorder in which antiplatelet autoantibodies cause the destruction of platelets, resulting in thrombocytopenia. In children, idiopathic thrombocytopenic purpura tends to be acute and short-lived, with only supportive management required. In most adults, however, the disorder is chronic and often requires medical therapy or splenectomy.¹⁻⁷ Splenectomy results in clinical improvement in about two thirds of patients with chronic idiopathic thrombocytopenic purpura, but it is not possible to predict reliably which patients will benefit from the procedure.³ A number of variables have been evaluated as possible predictive factors, including the response to corticosteroids,^{8,9} age, sex, and the pattern of clearance of radiolabeled platelets by the liver and spleen, but none have accurately predicted the result of splenectomy.¹⁰⁻¹³

Treatment with high-dose intravenous immune

globulin causes a transient rise in the platelet count in many patients with idiopathic thrombocytopenic purpura.^{2,3,14} This effect may be due, at least in part, to blockade of the Fc receptors of macrophages, particularly in the spleen.¹⁴⁻¹⁸ The blockade of Fc receptors by intravenous immune globulin prevents phagocytosis of antibody-coated platelets by splenic macrophages. In view of this mechanism, we hypothesized that patients who have good responses to immune globulin might also have good responses to splenectomy. In this report, we describe a series of 30 patients with idiopathic thrombocytopenic purpura who were treated with high-dose intravenous immune globulin and subsequently underwent splenectomy. We found that the response to intravenous immune globulin was a sensitive and specific predictor of the response to splenectomy.

METHODS

Patients

All the patients in this study had chronic idiopathic thrombocytopenic purpura, which was defined as thrombocytopenia (platelet count, <150,000 per cubic millimeter) that had persisted for a minimum of three months without other clinical or laboratory findings that could explain it. All the patients were treated with 2 g of intravenous immune globulin per kilogram of body weight (Miles Canada, Etobicoke, Ont.), administered in a dose of 1 g per kilogram over a period of six to eight hours, with the same dose repeated the next day. All the patients subsequently underwent either left subcostal open splenectomy or left lateral laparoscopic splenectomy.

Patients were excluded from the study if they had a positive serologic test for the human immunodeficiency virus (HIV) or risk factors for HIV infection, in the absence of test results; if they had systemic lupus erythematosus; or if they had not been treated with intravenous immune globulin before undergoing splenectomy.

Study Design

The study was a retrospective analysis of consecutive patients treated at McMaster University Medical Centre between 1984 and 1995 who met the eligibility criteria. Eligible patients were identified by searching the computerized patient-information data base at the center and by reviewing the records of one of us.

Response to Treatment

The responses to high-dose intravenous immune globulin and splenectomy were defined in the same way. An excellent response was defined as a platelet count that rose to a normal level

From the Departments of Surgery (C.L., M.M., P.T.), Pathology (N.H., J.G.K.), and Medicine (J.G.K.), McMaster University and the Hamilton Health Sciences Corporation, Hamilton, Ont., Canada. Address reprint requests to Dr. Kelton at Rm. 3W10, McMaster University Medical Centre, 1200 Main St. W., Hamilton, ON L8N 3Z5, Canada.

(>150,000 per cubic millimeter) after treatment. A good response was defined as a platelet count of 50,000 to 150,000 per cubic millimeter. A poor response was defined as a platelet count below 50,000 per cubic millimeter after treatment. We used a platelet count of 50,000 per cubic millimeter as the threshold for a good response because, in our experience, most patients with platelet counts at or above this level do not have bleeding or require therapy. The response to intravenous immune globulin was classified according to the response to the initial course. The platelet count was measured three to seven days after treatment. All patients were followed for a minimum of 12 months after surgery. Patients whose platelet counts fell below 50,000 per cubic millimeter and who required medical therapy for idiopathic thrombocytopenic purpura at any time after surgery were considered to have poor responses. Patients considered to have good or excellent responses to splenectomy received no additional medical therapy during follow-up.

Statistical Analysis

We calculated the specificity, sensitivity, and positive and negative predictive values of a response to intravenous immune globulin as a predictor of the response to splenectomy.

RESULTS

Patients

A search of the computer data base identified 82 consecutive patients who had received a diagnosis of idiopathic thrombocytopenic purpura and had undergone splenectomy at McMaster University Medical Centre between 1984 and 1995. Thirty-four patients were excluded because they did not receive intravenous immune globulin, 15 were excluded because another cause of thrombocytopenia was identified, and 3 had incomplete follow-up data.

Of the 30 eligible patients, 18 were female and 12 were male. The age range was 2 to 80 years at presentation. Nine patients were under the age of 15 years, and three were less than 6 (5, 4, and 2 years of age); the rest were adults.

Clinical manifestations of idiopathic thrombocytopenic purpura included purpura (in 80 percent of the patients), petechiae (in 63 percent), epistaxis (in 43 percent), gingival bleeding (in 10 percent), menorrhagia (in 7 percent), and gastrointestinal bleeding (in 6 percent). Twenty-seven of the patients had had thrombocytopenia for more than three months before undergoing splenectomy, and three (two adults and one child) had had thrombocytopenia for only three months when the surgery was performed. These three patients had poor responses to splenectomy, and chronic idiopathic thrombocytopenic purpura was subsequently diagnosed in all three.

Bone marrow examinations were performed in 14 of the 30 patients, and in all 14, the results were consistent with a diagnosis of idiopathic thrombocytopenic purpura. Antinuclear-antibody tests were performed in 20 patients (15 adults and 5 children), and all 20 had negative results. During follow-up, none of the patients had clinical or laboratory evidence of HIV infection or systemic lupus erythematosus.

Before undergoing splenectomy, all but two pa-

tients had received corticosteroid treatment, with variable responses. In addition, six patients had received intravenous anti-RhD immune globulin, two had been given danazol, two had undergone splenic irradiation, and one had received cyclophosphamide.

Twenty-seven patients underwent open splenectomy, and three underwent laparoscopic splenectomy. The pathological findings in spleen specimens from all 30 patients were consistent with the diagnosis of idiopathic thrombocytopenic purpura.

Response to Treatment

Nine patients had poor responses to high-dose intravenous immune globulin, 12 had good responses, and 9 had excellent responses. All patients had relapses within one month after receiving the first course of intravenous immune globulin. The responses to additional courses of intravenous immune globulin were less pronounced and lasted for shorter periods than the initial responses.

Table 1 shows the characteristics of the patients according to their responses to splenectomy. The responses were poor in 11 patients, good in 2, and excellent in 17. Of the 11 patients whose responses were classified as poor, 3 had no measurable response, 5 had relapses within 6 months after undergoing splenectomy, and 3 had relapses 6 to 14 months after surgery. All 11 patients received subsequent medical treatment. An accessory spleen was suspected in three of these patients; in two an accessory spleen was removed, but in the third no accessory spleen was found at laparotomy. Removal of the spleen was not beneficial in any of the patients. Subsequent investigations revealed bone marrow hypoplasia (diagnosed 16 months after splenectomy)

TABLE 1. CHARACTERISTICS OF 30 PATIENTS WITH IDIOPATHIC THROMBOCYTOPENIC PURPURA, ACCORDING TO THE RESPONSE TO SPLENECTOMY.

CHARACTERISTIC	RESPONSE TO SPLENECTOMY*	
	POOR (N=11)	GOOD OR EXCELLENT (N=19)
Ratio of men to women	5:6	7:12
Age (yr)	32.6±16.1	26.0±5.0
Response to corticosteroids (platelet count within 1 mo)	88,900±74,500	121,000±26,700
Response to intravenous IgG (platelet count within 7 days)	37,600±50,900	168,200±99,000
Time from diagnosis to splenectomy (yr)†	3.5±7.0	1.9±2.8
Time to relapse (mo)	4.8±5.1	—

*Responses are defined in the Methods section. Plus-minus values are means ±SD.

†For the three patients in whom the diagnosis of chronic idiopathic thrombocytopenic purpura was confirmed after surgery, the time to surgery was calculated from the time of the diagnosis of thrombocytopenia.

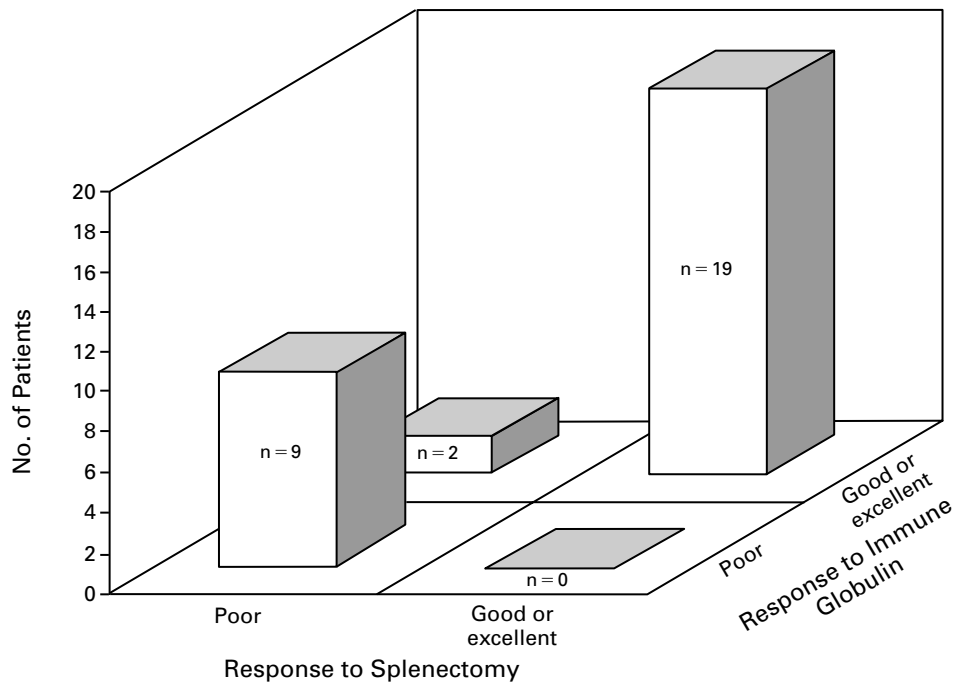


Figure 1. Response to Intravenous Immune Globulin in Relation to the Response to Splenectomy at One Year in 30 Patients with Idiopathic Thrombocytopenic Purpura.

A poor response was defined as a platelet count lower than 50,000 per cubic millimeter, a good response as a platelet count of 50,000 to 150,000 per cubic millimeter, and an excellent response as a platelet count higher than 150,000 per cubic millimeter. All the patients who had poor responses to intravenous immune globulin also had poor responses to splenectomy, and all the patients who had good or excellent responses to intravenous immune globulin had good or excellent responses to splenectomy.

in one of these three patients and an abnormal bone marrow karyotype — XYdel(13)(q32) in 4 of 20 cells — of unknown relevance in another patient. No evidence of systemic lupus erythematosus or another condition that could explain the persistent thrombocytopenia was found in the patients with poor responses to splenectomy.

None of the 19 patients with good or excellent responses required further treatment. Follow-up of these 19 patients ranged from 12 months (in 13 patients) to 8 years.

Relation between Responses to Intravenous Immune Globulin and Splenectomy

There was a close relation between the response to high-dose intravenous immune globulin and the outcome of splenectomy (Fig. 1). Figure 2 shows the clinical courses in two representative patients: one with excellent responses to both intravenous immune globulin and splenectomy, and one with poor responses to both treatments. All nine patients who had poor responses to high-dose intravenous immune globulin also had poor responses to splenectomy. In contrast, of the 21 patients who had good or excellent responses to intravenous immune globulin, 19 had good or excellent responses to sple-

nectomy. Two patients had poor responses to splenectomy despite a good or excellent response to intravenous immune globulin.

The sensitivity of the response to intravenous immune globulin as a predictor of the response to splenectomy was 100 percent, and the specificity was 81.8 percent, with a positive predictive value of 90.5 percent and a negative predictive value of 100 percent.

DISCUSSION

Idiopathic thrombocytopenic purpura affects both children and adults. The childhood form of the disorder is acute and self-limited in 80 percent of cases, whereas at least 80 percent of cases in adults are chronic. Splenectomy produces a long-term remission or cure in approximately two thirds of patients,^{1-3,5-7} but surgery is seldom performed in young children because of the risk of septicemia and cannot be performed in some elderly patients with other medical problems. Vaccination against encapsulated organisms¹⁹ and laparoscopic splenectomy²⁰ have dramatically reduced the morbidity associated with the procedure. Consequently, splenectomy is now feasible for a relatively large proportion of children and adults with idiopathic thrombocytopenic pur-

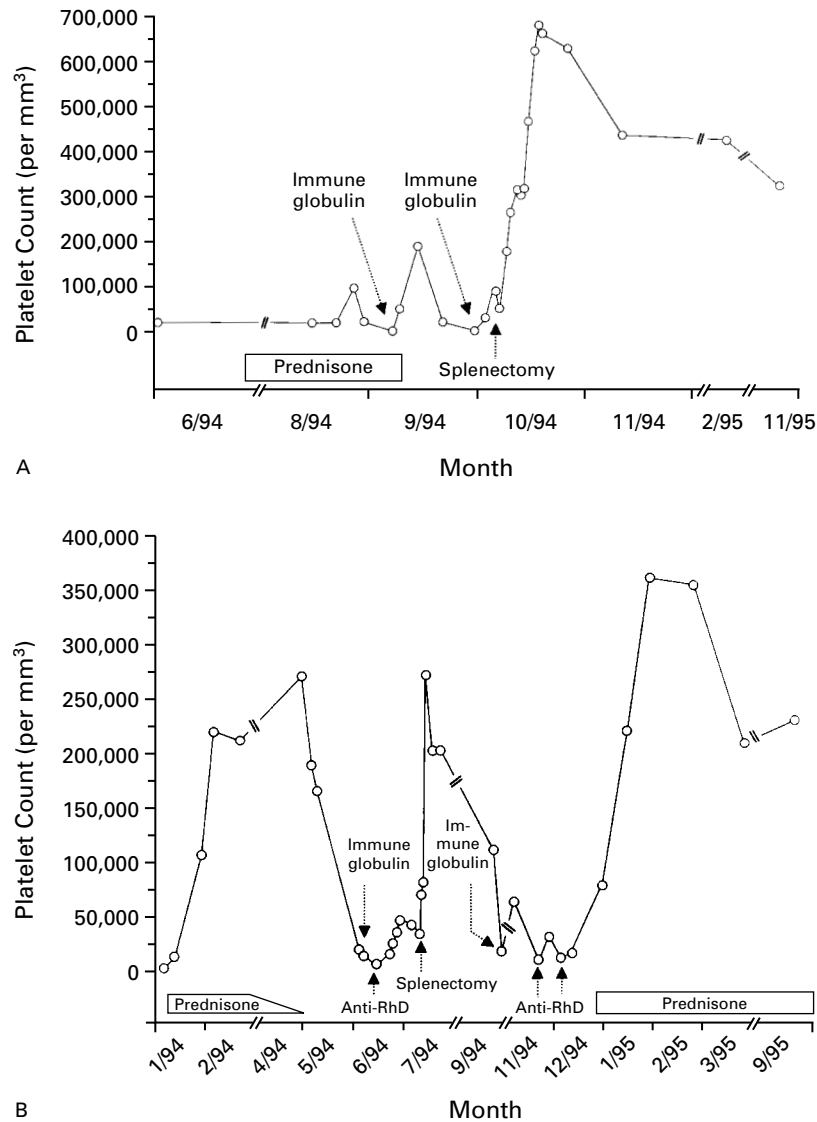


Figure 2. Platelet Counts in Two Patients with Idiopathic Thrombocytopenic Purpura Treated with Intravenous Immune Globulin and Splenectomy.

Panel A shows the clinical course in a 54-year-old man who had excellent responses to intravenous immune globulin on two occasions before undergoing splenectomy, which also produced an excellent response. One year later, in the absence of treatment, his platelet count ranged from 300,000 to 400,000 per cubic millimeter. Panel B shows the clinical course in a 32-year-old woman who had a good response to prednisone but poor responses to intravenous immune globulin and splenectomy. After the splenectomy, prolonged treatment with prednisone kept the platelet count at a safe level. Anti-RhD denotes anti-RhD immune globulin.

pora. Nonetheless, it is not without adverse effects, even when performed at centers with extensive experience.^{5,6} A way of predicting the response to splenectomy would therefore be helpful in making treatment decisions.

High-dose intravenous immune globulin temporarily elevates the platelet count in many patients with idiopathic thrombocytopenic purpura.¹⁴⁻¹⁸ One mechanism underlying this effect is the blockade of

Fc receptors on phagocytic cells in the spleen.¹⁴⁻¹⁷ Theoretically, high-dose intravenous immune globulin produces the equivalent of a temporary medical splenectomy, which suggests that the response to this treatment can predict the response to surgical splenectomy.

In the 30 patients in our study, the responses to intravenous immune globulin were similar to the responses to splenectomy. All nine patients who had

poor responses to intravenous immune globulin also had poor responses to splenectomy. These nine patients subsequently required intermittent or continuous medical therapy to maintain their platelet counts at a level above 50,000 per cubic millimeter. Of the 21 patients who had good or excellent responses to intravenous immune globulin, 19 also had good or excellent responses to splenectomy. Our retrospective study is too small to allow conclusions about differences in responses between adults and children with idiopathic thrombocytopenic purpura.

We suggest that physicians consider early splenectomy rather than a long-term course of corticosteroids for patients with good or excellent responses to intravenous immune globulin. Perhaps the response to high-dose intravenous immune globulin can also be used to make decisions about treatment in young and elderly patients, in whom splenectomy is frequently deferred because of concern about the risk associated with surgery or the immunologic consequences.

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