

Effect of intravenous gammaglobulin (IVIG) on the platelet count in patients with Wiskott-Aldrich syndrome

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The ability of IVIG to increase platelet counts in patients with idiopathic thrombocytopenic purpura suggests its potential usefulness in other disease states characterized by low platelet counts. This possibility was evaluated in nine patients with the Wiskott-Aldrich syndrome (WAS) who received IVIG, at a dose of 400 mg/kg every 4 weeks. The mean platelet count prior to institution of IVIG was 32,000/cumm (range 2,400 to 98,000). Following administration of IVIG, the platelet count ranged between 5,000 and 85,000/cumm. There were no immediate increases in platelet counts after IVIG infusion in any patient who had serial platelet counts. During treatment, patients were not given any routine platelet transfusions for low platelet counts. However, while on IVIG, two patients showed a good response to platelet transfusion prior to surgical procedures. In conclusion, chronic IVIG therapy does not appear to affect platelet counts in patients with the Wiskott-Aldrich syndrome.

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The Wiskott-Aldrich syndrome (WAS), first described by Wiskott in 1937 and Aldrich in 1954 (1, 2), is a rare X-linked form of immunodeficiency characterized by the triad of eczema, thrombocytopenia with decreased mean platelet volume, and increased susceptibility to pyogenic and opportunistic infections (1–5). Patients also have an increased risk of malignancy, primarily acute leukemia, lymphoma, and solid tumors of the CNS (5). In the fully expressed form, the diagnosis is evident within the first year of life and, until recently, has been almost invariably fatal in infancy or early childhood (6). The etiology of the defect in WAS remains unknown. In 1987, Peacocke & Siminovitch, and later Kwan et al, using restriction fragment length polymorphisms (RFLPs) and appropriate families, reported close linkage between the WAS gene and two loci, DXS14 (Xp11) and DXS7 (Xp11.3), which map to the proximal short arm of the X chromosome (7, 8).

The thrombocytopenia in WAS is usually present from birth resulting in rectal bleeding in the newborn period as the most common presentation, and later, many patients are at risk of life-threatening intracranial, pulmonary or gastrointestinal hemorrhage (2, 3, 5, 6). Management of this thrombocytopenia poses a difficult clinical problem.

Intravenous gammaglobulin (IVIG) has been used therapeutically in patients with acute and chronic idiopathic thrombocytopenic purpura (ITP) (9, 10). The therapy is associated with minimal side effects. Platelet count increases, but prolonged, unsustained remissions occur infrequently. A role for an immune-mediated mechanism in WAS-associated thrombocytopenia has been suggested by the observation that WAS platelets are coated with increased amounts of immunoglobulins relative to normal platelets (11). The role of IVIG in the therapy of WAS-associated thrombocytopenia has not been thoroughly explored before. We report our experience with IVIG therapy in this group of patients.

Material and methods

We reviewed charts of all patients with the diagnosis of WAS seen at St. Jude Children's Research Hospital to identify patients who had received treatment with IVIG. The diagnosis of WAS was based on the following criteria: 1) onset of disease before one year of age; 2) thrombocytopenia with small platelets; and 3) clinical or laboratory evidence of immunodeficiency, i.e. recurrent bacterial infections, abnormal serum immunoglobulins, and/or abnormal lymphocyte numbers or function. Platelet counts ob-

Table 1. Summarizing the pre- and post IVIG platelet counts in our Wiskott-Aldrich patients.

Pt #	PreIVIG platelet count ($\times 10^9/L$) Range (median)	PostIVIG platelet count ($\times 10^9/L$) Range (median)	Duration IVIG (months)
1	19- 50 (20)	18-48 (36)	16
2	34- 90 (50)	24-48 (36)	13
3	15- 52 (39)	17-36 (19)	30
4	15- 98 (47)	10-87 (35)	52
5	33- 85 (51)	17-85 (26)	18
6	16- 53 (30)	19-30 (27)	6
7	15- 87 (30)	8-52 (22)	42
8	2.4- 5 (5)	5-32 (14)	42
9	7-100 (22)	12-28 (22)	55

tained as part of the patients routine follow-up care were noted, as well as any record of platelet transfusions. Platelet counts were obtained routinely at each clinic visit (usually four weeks after the most recent IVIG therapy). Platelet counts were done on the S+Stkr Coulter, Coulter Corporation, Hialeah, FL. Complications related to low platelet counts, or infusion of IVIG were noted. IVIG preparations used were either 5% Venoglobulin, Alpha Therapeutic Corporation, Los Angeles, CA; or 10% Gamimmune, Miles Inc, Elkhart, IN. Platelet counts obtained immediately before and after IVIG, if available, were also recorded.

Results

Twelve patients with the diagnosis of WAS or WAS variant were treated in the Immunodeficiency Clinic

at St. Jude Children's Research Hospital from 1990 to 1994. The patients ranged in age from 3.5 months to 75 months (median, 12 months) at the time of referral. Four of the 12 patients (Table 1, Pts 3, 4, 6 and 8) had been previously diagnosed as having acute or chronic idiopathic thrombocytopenic purpura (ITP), and a third, a girl (Pt 9), had been given the diagnosis of myelodysplastic syndrome. All four patients who had been given a preliminary diagnosis of ITP had received high dose IVIG therapy (1 g/kg/day for two days in Patient 6, and 400 mg/kg/day for 3-5 days in Patients 3, 4, and 8) and although sequential platelet counts were not available, the therapy was considered ineffective.

It was our policy to treat patients with WAS and recurrent infections and/or defective antibody production with chronic prophylactic antibiotics and 400 mg/kg of IVIG each month. Splenectomy was reserved for patients with intractable hemorrhage; however, three patients including one of the patients who had been diagnosed as having chronic ITP, had undergone splenectomy prior to referral. If patients had an HLA-matched sibling, bone marrow transplantation was recommended.

Nine of the 12 patients were treated with IVIG. Two of the patients who did not receive IVIG expired during their diagnostic evaluation. The third patient who did not receive IVIG, was the younger brother of Patient 8, and did not experience recurrent infections. Profound to moderate thrombocytopenia was noted in all the patients prior to the initiation of IVIG therapy (range 2.4-100 $\times 10^9/L$ - Table 1). In splenectomized patients, the platelet counts shown in the table were obtained prior to splenectomy.

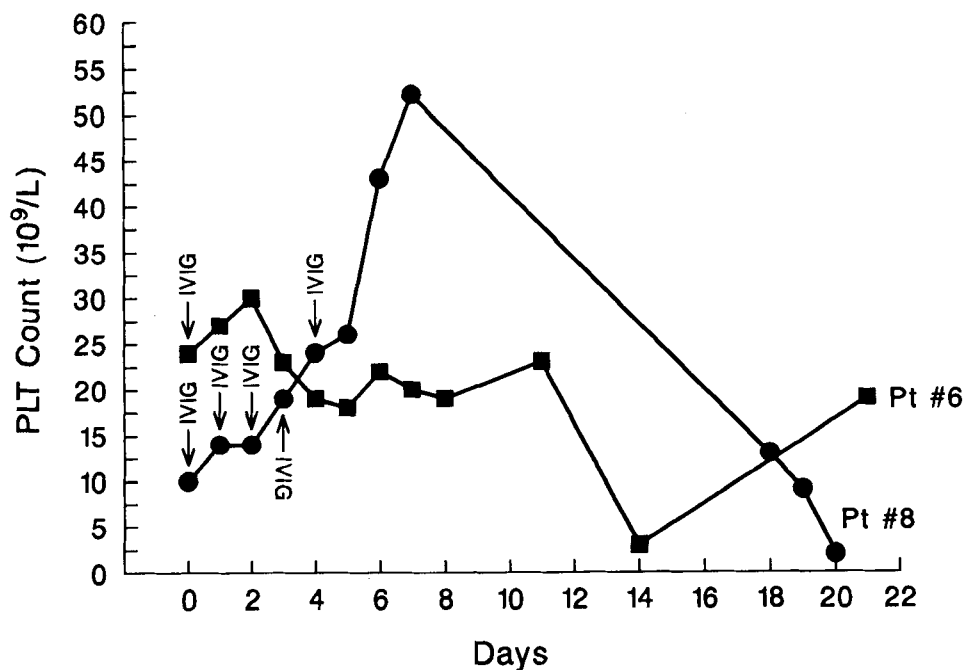


Fig. 1. Platelet counts in Patient 6 who received a single dose of IVIG, and Patient 8 who received 5 daily doses of 0.4 gm/kg.

Platelet counts obtained after initiation of IVIG therapy (duration, 6 months – 4.5 years; median, 30 months) were equally low (range, $5\text{--}85 \times 10^9/\text{L}$). Platelet counts were done at each clinic visit, four weeks after the most recent IVIG therapy.

Only Patient 4, experienced significant hemorrhage while receiving IVIG. At 27 months of age, the patient's spleen was removed after he experienced 2 episodes of life threatening epistaxis at age 25 and 26 months respectively, with platelet counts as low as $5 \times 10^9/\text{L}$. Postsplenectomy, the patients' platelet counts remained low. The patient was continued on IVIG therapy on a monthly schedule and after 24 months his platelet count spontaneously rose to $102\text{--}250 \times 10^9/\text{L}$. Patient 5 had splenectomy at 18 months of age for persistent thrombocytopenia at the referring institution, following which his platelet counts rose to the normal range and remained so till his death. Patient 6, at age 24 months, developed Coombs-positive hemolytic anemia and neutropenia while receiving IVIG, and was treated with oral steroids. Over a 6-week period the anemia and neutropenia resolved, but the platelet count was not affected by this treatment (Fig 1). Patient 8, whose spleen was removed when he was thought to have chronic ITP, had platelet counts of $3\text{--}32 \times 10^9/\text{L}$ prior to splenectomy and $27\text{--}222 \times 10^9/\text{L}$ after surgery. Nine years after splenectomy, he developed pancytopenia associated with a direct positive Coombs. Like Patient 6, he was treated with oral steroids and in addition received 400 mg/kg IVIG every day for 5 days. As shown in Fig. 1, the platelet count did not change immediately in response to this therapy.

Two of the patients received platelet transfusions prior to surgical procedures (Patient 7, for dental procedures and Patient 6, for a hernia repair) while on monthly IVIG. Their immediate post transfusion platelet counts were $114 \times 10^9/\text{L}$ and $158 \times 10^9/\text{L}$ respectively. Infusion of IVIG was well tolerated by all but Patient 7. This patient received IVIG infusion for one year without problems, then developed chills, cyanosis and transient hypotension on repeated occasions during the infusion of IVIG. These symptoms were alleviated by premedication with steroids and antihistamines prior to each infusion.

Three of the patients with WAS died during the course of this study. As noted above, two patients died during the initial evaluation period. One, a five-month-old child, died of retroperitoneal hemorrhage; the second, a six-year-old boy whose spleen had been removed at another center, died of pneumococcal sepsis. Patient 5, who had had a splenectomy at the referral center, also expired from pneumococcal sepsis. Compliance with chronic prophylactic antibiotics was incomplete in both the latter two patients. After splenectomy, Patient 8 developed multiple episodes of pneumococcal sepsis with one epi-

sode of septic shock from which he was successfully resuscitated.

Discussion

There are several factors that may contribute to the thrombocytopenia seen in patients with WAS. Several authors have reported data suggesting ineffective production and/or production of an intrinsically abnormal platelet (12–14). Studies of platelet survival suggest that the thrombocytopenia is mainly due to increased peripheral destruction due to expression of abnormal cell surface glycoproteins, suggesting an immune component to the thrombocytopenia (11, 15). Past studies have indicated that glucocorticoids have little or no effect on platelet counts in patients with WAS (12). Our study demonstrates that IVIG is also ineffective in treating thrombocytopenia in these patients.

Studies by Corash et al., and by Lum et al., have shown that splenectomy may result in normalization of platelet size and platelet count in a high percentage of patients (11, 15). In a long-term follow-up of 39 patients who underwent splenectomy for management of their thrombocytopenia, Mullen et al. noted normalization of platelet counts in nearly all patients and a sevenfold decrease in the rate of serious bleeding (16). Only Patient 5 had any significant rise in platelet count post-splenectomy. However, it is not without risks, especially the risk of pneumococcal sepsis (15, 17), as was seen in three of our patients, and recurrence of thrombocytopenia after splenectomy is a common problem (11).

Bone marrow transplantation (BMT) of compatible bone marrow has been successful in some patients, but suitable donors are not always available (16, 18, 19). Only one of our 12 patients had a HLA-matched donor. In a long-term follow-up study of 62 cases of WAS, 19 of whom were treated with BMT, 12/12 patients receiving HLA-matched sibling marrow achieved satisfactory hematological and immunological reconstitution. By contrast, only 2 of 7 patients receiving haploidentical, parental or matched unrelated marrow survived more than one year after transplantation (16).

Case reports have suggested that IVIG can increase the platelet count in WAS (9, 20). Wodzinski et al. reported on a single patient with WAS and varicella infection, who received a 3-day course of IVIG (20). The patient showed a dramatic increase in platelet count (from $<10 \times 10^9/\text{L}$ to $102 \times 10^9/\text{L}$) two days after receiving IVIG. But the counts dropped to $<10 \times 10^9/\text{L}$ in one week. Our data does not support this rise in platelet count; in fact, none of the patients in our series showed such a dramatic increase in their platelet counts immediately after receiving IVIG.

However, a good response to platelet transfusion was noted in the two patients who received them while on IVIG. This has been reported previously in patients with ITP (21), and may be due to direct monocyte-macrophage system Fc-receptor blockade or by blocking antiplatelet antibody by anti-idiotypic antibodies present in the IVIG preparations. Hence, in certain situations where an acute increase in platelet count is required (as in pre or intraoperative states), IVIG with platelet transfusions may help in bringing up the platelet counts to a level where the surgical procedure can be safely performed.

Atypical or WAS variants have been reported in the literature (22–24), and the only female patient in our series who has been reported before (24), may reflect this variant. Interestingly, this patient also did not show any rise in platelet counts during IVIG therapy.

IVIG is expensive and although IVIG did not increase platelet count, we do feel that it is beneficial to these patients. Its use has significantly decreased the frequency of pyrogenic infections (25) in these patients, and has improved their quality of life. Hence its use in these patients may be cost effective. However, as a therapeutic modality for WAS-associated thrombocytopenia, it does not seem to affect the platelet counts in these patients in a significant manner as it does in patients with ITP.

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References

1. WISKOTT A. Familiärer, angeborener Morbus Werlhofii? Monatsschrift Kinderheilkunde 1937; 68: 212–6.
2. ALDRICH RA, STEINBERG AG, CAMPBELL DC. Pedigree demonstrating a sex-linked recessive condition characterized by draining ears, eczematoid dermatitis and bloody diarrhea. Pediatrics 1954; 13: 133–9.
3. MURPHY S, OSKI FA, NAIMAN JL, LUSCH CJ, GOLDBERG S, GARDNER FH. Platelet size and kinetics in hereditary and acquired thrombocytopenia. N Engl J Med 1972; 286: 499–504.
4. CONLEY ME. Molecular approaches to analysis of X-linked immunodeficiencies. Annu Rev Immunol 1992; 10: 215–8.
5. PERRY GS, SPECTOR BD, SCHUMAN LM, et al. The Wiskott-Aldrich syndrome in the United States and Canada (1892–1979) J Pediatr 1980; 97: 72–8.
6. STANDEN GR. Wiskott-Aldrich syndrome: new perspectives in pathogenesis and management. J Royal Coll Physicians (London 1988); 22: 80–3.
7. PEACOCKE M, SIMINOVITCH KA. Linkage of the Wiskott-Aldrich syndrome with polymorphic DNA sequences from the human X chromosome. Proc Natl Acad Sci USA 1987; 84: 3430–33.
8. KWAN SP, SANDKUHL LA, BLAESE M, et al. Genetic mapping of the Wiskott-Aldrich syndrome with two highly linked polymorphic DNA markers. Genomics 1988; 3: 39–43.
9. IMBACH P, D'APUZZO V, HIRT A, et al. High dose intravenous gammaglobulin for idiopathic thrombocytopenic purpura in childhood. Lancet 1981; 1: 1228–31.
10. BUSSEL JB, KIMBERLY RP, INMAN RD, et al. Intravenous gammaglobulin treatment of chronic idiopathic thrombocytopenic purpura. Blood 1983; 62: 480–6.
11. CORASH L, SHAFFER B, BLAESE RM. Platelet-associated immunoglobulin, platelet size, and the effect of splenectomy in the Wiskott-Aldrich syndrome. Blood 1985; 65: 1439–43.
12. GROTTUM KA, HOVIG T, HOLMSEN H, ABRAHAMSEN AF, JEREMIC M, SEIP M. Wiskott-Aldrich syndrome: qualitative platelet defects and short survival. Br J Haematol 1969; 17: 373–88.
13. OCHS HD, SLICHTER SJ, HARKER LA, VON BEHRENS WE, CLARK RA, WEDGEWOOD RJ. The Wiskott-Aldrich syndrome: studies of lymphocytes, granulocytes and platelets. Blood 1980; 55: 243–52.
14. VERHOEVEN AJ, VAN-OOSTRUM IE, VAN-HAARLEM H, AKKERMANN JW. Impaired energy metabolism in platelets from patients with the Wiskott-Aldrich syndrome. Thromb-Haemost 1989; 61: 10–14.
15. LUM LG, TUBERGEN DG, CORASH L, BLAESE RM. Splenectomy in the management of the thrombocytopenia of the Wiskott-Aldrich syndrome. N Engl J Med 1980; 302: 892–6.
16. MULLEN CA, ANDERSON KD, BLAESE RM. Splenectomy and/or bone marrow transplantation in the management of the Wiskott-Aldrich syndrome: long term follow-up of 62 cases. Blood 1993; 82: 2961–66.
17. STANDEN GR, ORCHARD JA, HUTTON RD. Wiskott-Aldrich syndrome: fatal consequences of splenectomy in an unrecognized attenuated variant. Br J Clin Prac 1990; 44: 338–9.
18. PARKMAN R, RAPPAPORT JM, GEHA R. Complete correction of the Wiskott-Aldrich syndrome by allogeneic bone marrow transplantation. N Engl J Med 1978; 298: 921–7.
19. RIM JJ, RAPPAPORT JM. Bone marrow transplantation for the Wiskott-Aldrich syndrome. Long-term follow-up. Transplantation 1990; 50: 617–20.
20. WODZINSKI MA, LILLEYMAN JS. High-dose immunoglobulin therapy of Wiskott-Aldrich syndrome. Pediatr Hem Oncol 1987; 4: 345–8.
21. BAUMANN MA, MENITOVE JE, ASTER RH, ANDERSON T. Urgent treatment of idiopathic thrombocytopenic purpura with single-dose gammaglobulin infusion followed by platelet transfusion. Ann Intern Med 1986; 104: 808–9.
22. CANALES ML, MAUER AM. Sex-linked hereditary thrombocytopenia as a variant of Wiskott-Aldrich syndrome. N Engl J Med 1967; 277: 899–901.
23. EVANS DI, HOLZEL A. Immune deficiency state in a girl with eczema and low serum IgM. Possible female variant of Wiskott-Aldrich syndrome. Arch Dis Child 1970; 45: 527–33.
24. CONLEY ME, WANG WC, PAROLINI O, SHAPIRO DN, CAMPANA D, SIMINOVITCH KA. Atypical Wiskott-Aldrich syndrome in a girl. Blood 1992; 80: 1264–69.
25. BUCKLEY RH. Long-term use of intravenous globulin in patients with primary immunodeficiency diseases: inadequacy of current dosage practices and approaches to the problem. J Clin Immunol 1982; 2: 155–215.