Hemolytic transfusion reactions after administration of intravenous immune (gamma) globulin: a case series analysis

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BACKGROUND: This case series summarizes our observations of hemolytic reactions after the administration of large amounts of intravenous immune (gamma) globulin (IVIG).
STUDY DESIGN AND METHODS: Cases of hemolysis were identified by a decrease in hemoglobin not otherwise explained following IVIG administration.
RESULTS: Sixteen cases were identified over a 21/2-year period at the Ottawa Hospital of approximately 1000 patients receiving IVIG (1.6%). Characteristics of these patients include a large dose of IVIG, female sex, non-O blood group, and underlying inflammatory state.
CONCLUSIONS: Significant hemolysis may occur after the administration of large doses of IVIG. A two-step mechanism of hemolysis is proposed, sensitization by ABO isohemagglutinins followed by phagocytosis by activated macrophages. A simple protocol to facilitate the early detection of such cases is presented.

Intravenous immune (gamma) globulin (IVIG), first introduced for the treatment of primary immunodeficiencies, is currently used in a wide range of other disorders.[1] The more common adverse reactions associated with the use of IVIG include volume overload, allergic reactions, and pulmonary reactions.[1] The passive transfer of blood group alloantibodies, including anti-A, -B, -D, and -K, has been reported to cause positive direct antiglobulin test after IVIG administration.[2] Clinically significant hemolysis associated with IVIG administration is rare. Recently, however, a number of severe hemolytic reactions associated with the use of IVIG have been reported.[3,4] Mild to moderate hemolysis can be easily missed and the true incidence of such reactions is difficult to document without careful clinical and laboratory follow-up. Mild hemolytic reactions may be of little clinical significance and are outweighed by the benefits of IVIG.

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CASE SERIES

We report 16 cases of hemolytic transfusion reactions associated with the administration of IVIG (Gamunex, Talecris Biotherapeutics, Inc., Research Triangle Park, NC; Gammagard, Baxter Healthcare Corp., Deerfield, IL; or IGIVnex, Talecris Biotherapeutics). The individual patient characteristics are summarized in Table 1, and patient characteristics predisposing to IVIG-related hemolysis are summarized in Table 2. The percentage of different commercial preparations of IVIG associated with the hemolytic reactions closely correlates with our inventory in the transfusion medicine laboratory, where Gamunex constitutes 87 percent and Gammagard 13 percent of the inventory. In our case series, 11 patients (11/16, 69%) received Gamunex, 3 patients (3/16, 19%) received Gammagard, 1 patient (1/16, 6%) received IGIVnex, and 1 patient (1/16, 6%) received mostly Gamunex but also a small amount of Gammagard. All cases showed evidence of hemolysis after IVIG infusion, with a decrease in hemoglobin (Hb) in 15 of 16 (94%) or lower than expected increase in Hb after red cell (RBC) transfusion (1/16, 6%, Case 5). The mean decrease in Hb was 32 g per L (range, 8-52 g/L). Hemolysis associated with the administration of IVIG was observed from 12 hours to 10 days after the first dose of IVIG, with the nadir Hb level occurring from 1 day to 2 weeks after the last dose of IVIG. Figure 1 shows representative plots of Hb level versus time for Cases 10 and 11. In both cases, the Hb level decreased by approximately 50 g per L, with the lowest Hb level documented

TABLE 1. Individual patient characteristics

Case	Age (years), sex	Diagnosis	IVIG total amount (g)	Brand of IVIG	Blood group	DAT	Eluate and/or plasma	Decrease in Hb (g/L)	Hemolysis requiring RBC transfusion	Number of inflammatory markers*
1	27, F	Gestational ITP	50	Gammagard	AB–	Negative	Anti-A	14	No	1
2	50, F	Guillain-Barré syndrome	200	Gamunex	A+	Negative	ND	36	No	1
3	36, F	Sepsis (*Streptococcus pyogenes*)	120	Gamunex	O–	Positive polyspecific	See text	43	Yes (2 units)	1
4	66, F	Guillain-Barré syndrome	100	Gamunex	AB+	Weak+ IgG	Negative	36	No	3
5	61, F	Postoperative necrotizing fasciitis	120	Gammagard	B+	1+ IgG	Anti-B	†	No	4
6	51, F	Postoperative necrotizing fasciitis	100	Gamunex	A+	Weak+ IgG, 1+ complement	Anti-A	32	No	4
7	44, F	HIV+, CAH, sepsis	315	Gamunex + Gammagard	B+	Weak+ IgG	Anti-B	34	No	6
8	71, M	Rhabdomyolysis	200	Gamunex	A+	Weak+ IgG	Anti-A	30	No	1
9	19, F	Viral meningitis with postinfectious Guillain-Barré syndrome	180	Gamunex	A+	Weak+ IgG	Anti-A	47	No	1
10	23, F	ITP	210	Gamunex	B+	Weak+ IgG	Anti-B	51	No	0
11	60, M	Guillain-Barré syndrome	200	Gamunex	A+	Weak+ IgG	Anti-A	50	No	2
12	18, F	Viral encephalitis	120	Gamunex	B+	Weak+ IgG	Negative	24	Yes (1 unit)	3
13	60, M	Postoperative necrotizing fasciitis	350	IGIVnex	A+	3+ IgG	Anti-A	8	No	1
14	55, M	Guillain-Barré syndrome	300	Gammagard	B+	Weak+ IgG	Negative	52	No	2
15	22, M	Systemic lupus	285	Gamunex	B+	Weak+ IgG	Auto‡	13	Yes (3 units)	4
16	49, M	Guillain-Barré syndrome	295	Gamunex	A+	1+ IgG	Anti-A	30	No	3

* Inflammatory markers include haptoglobin, ferritin, fibrinogen, D-dimer, erythrocyte sedimentation rate, C-reactive protein, or decreased serum albumin.
† Ongoing RBC transfusions resulted in an increase of 19 g per L, but this increment is less than expected.
‡ Eluate demonstrated warm auto-antibodies.
CAH = cold agglutinin hemolysis; ITP = immune thrombocytopenic purpura; ND = not done.

TABLE 2. Summary of patient characteristics predisposing to IVIG-related hemolysis

Characteristics seen in >50% of cases	Number of patients (%)
High cumulative dose of IVIG	15/16 (94)
Non-O blood group	15/16 (94)
Female	10/16 (63)
Positive inflammatory serologic marker	15/16 (94)

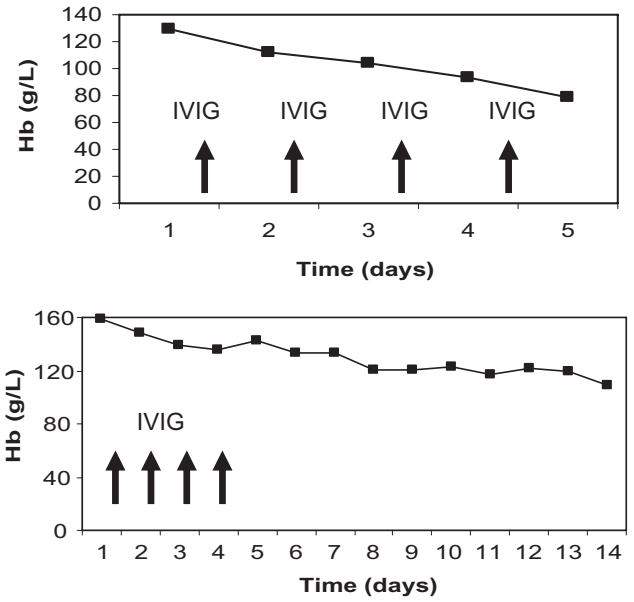

Fig. 1. Representative time courses of decrease in Hb after IVIG administration (Case 10, top; and Case 11, bottom).

1 day (Case 10) or 10 days (Case 11), after the last dose of IVIG. No other cause for the decrease in Hb level was identified. Neither of these patients received RBC transfusion. The 3 patients requiring RBC transfusion due to IVIG-related hemolysis (Cases 3, 12, and 15), received the RBC units from 2 to 6 days after the last dose of IVIG. Spherocytes were noted in 12 of 16 (75%) cases. A positive direct antiglobulin test (DAT) was shown in 14 of 16 (88%) cases. The majority of the positive DAT results were immunoglobulin G (IgG) only (12/14, 86%). Only 1 case (1/14, 7%) showed positivity for both IgG (weak positive) and complement (1+), and this patient (Case 6) also received RBCs and frozen plasma transfusions at the same time as the IVIG. Case 3 was only tested with polyspecific DAT reagent. Most of the DAT results were weakly positive or 1+ positive (12/14, 86%), with only 1 case showing 3+ positive (Case 13). Anti-A or anti-B antibodies were detected in the patients' plasma and/or eluate in 10 of 16 (63%) cases.

In 10 patients (Cases 1, 2, 4, 8, 9, 10, 11, 12, 14, and 16), the association between IVIG administration and hemolysis is clear. In 6 patients (Cases 3, 5, 6, 7, 13, and 15), the interpretation of the data is more difficult, with the decrease in Hb less definitively linked to IVIG administration. Disseminated intravascular coagulation was a coexisting morbidity in 2 patients (Cases 5 and 7) and may have contributed to hemolysis. The decrease in Hb in Cases 3 and 13 may be attributed to a combination of intraoperative blood loss and dilutional effect, compounded by fluid retention due to oligouric acute renal failure. Case 3 is the only group O patient in the series: in vitro testing of this patient's RBCs with IVIG resulted in hemolysis of the patient's RBCs. The transfusion of platelets with ABO-incompatible plasma in Case 5 may be a cause of the anti-B in the eluate. Cases 6 and 7 had significant comorbidities, with elevation of total bilirubin and lactate dehydrogenase (LDH); but a significant decrease in Hb was observed during the course of the IVIG infusion. The positive DAT results observed in Cases 6 and 7 may possibly be attributed to passive transfer of ABO antibodies during the transfusion of group O RBCs and to warm autoimmune hemolytic anemia in Case 15. We examined the titers of isohemagglutinins in the IVIG products used in our hospital and found them to be well within recommended levels, with an anti-A titer of 4 to 8 and an anti-B titer of 2 to 4. The majority of patients that were tested showed evidence of an inflammatory physiologic state, with elevation of ferritin (9/11, 82%), elevation of fibrinogen (4/8, 50%), decreased serum albumin (12/15, 80%) and elevated erythrocyte sedimentation rate and/or C-reactive protein (7/9, 78%). Nine cases had diagnostic imaging of the abdomen, and in none of these cases was splenomegaly documented. As an acute-phase reactant, serum haptoglobin was elevated in 2 of 10 (20%) cases, normal in 4 of 10 (40%) cases, and decreased in only 4 of 10 (40%) cases. All patients, except Case 10 (15/16, 94%) demonstrated at least one serologic marker of an inflammatory state. Secretory status was assessed indirectly by Lewis phenotyping in only 3 patients, with 2 secretors (Le(a–b+), Cases 8 and 14) and 1 nonsecretor (Le(a+b–), Case 16) identified.

DISCUSSION

Our case series of IVIG-related hemolysis suggests that certain characteristics may be associated with an increased risk of this complication. Hemolytic reactions may be particularly associated with high-cumulative-dose IVIG therapy.[5-7] This was noted in our case series, with 15 of 16 (94%) patients receiving 100 g or more in 2 to 4 days. The preponderance of non-O blood group in our series suggests a role for passive transfer of ABO isohemagglutinins in the hemolytic reaction.[2] We documented, however, that the titers of isohemagglutinins in the IVIG preparations in use in our laboratory (from 2 to 8) are well within those recommended by the European Pharmacopoeia, which recommend that no anti-A and anti-B hemagglutinins are detectable at the 1 to 64 dilution.[8] There is an overrepresentation of group B and AB patients

in our case series (8/16, 50%). Soluble ABO blood group substance may play a role in neutralizing isohemagglutinins. Individuals of AB, or non-A1, blood group and nonsecretors might be more prone to hemolysis, because less A soluble substance in the plasma is available to neutralize anti-A.[9] Individuals of B blood group might also be more prone to hemolysis, because it may be that less B substance is secreted. Only 3 patients were Lewis phenotyped (2 secretors and 1 nonsecretor) and the soluble ABO blood group substances were not assessed. Further studies are required to address this theory. The majority of the positive DAT results were IgG only. The IgG subclasses IgG1 and IgG3 are associated with the ability to fix complement. Testing for the subtypes of IgG in the IVIG preparations was not performed and this is another area for further investigation. The reason for the preponderance of female recipients is not certain. Multiparous females are more likely to have antibodies that have been linked to transfusion-associated acute lung injury (TRALI). Could their primed immune systems be more likely to react with the high-molecular-weight moieties present in IVIG, that have been found to activate complement and bind RBCs?[10] There was serologic evidence of the presence of inflammatory process in all but one of our cases, which may enhance phagocytosis of sensitized RBCs. Similar to the pathogenesis of TRALI, we propose a two-hit mechanism for the development of clinically significant hemolysis after IVIG infusion.[11] The first step is the passive transfer of ABO isohemagglutinins to non-O blood group patients. The second step is the enhanced activity of the immune system in patients with an underlying inflammatory state, with accelerated removal of sensitized RBCs from the circulation. Some of the more recent reports of IVIG-associated hemolytic reactions have occurred in patients with inflammatory conditions (pneumonia, Kawasaki disease),[4,6] and the majority of our cases had serologic evidence of inflammation.

It is difficult to predict the occurrence of hemolytic reactions associated with IVIG infusion. Cross-matching before infusion has been recommended, to identify batches that might cause hemolysis in the recipient.[7] Another suggested strategy is to develop guidelines for preventing hemolysis, based on an algorithm incorporating antibody titer and IVIG dose.[2] Anti-A titers of greater than 1 in 16 are more likely to cause hemolysis of clinical significance.[5] Our recommendation is to perform pretransfusion testing before the start of the infusion and to perform posttransfusion testing within 36 hours after the first infusion, which would include DAT (and eluate if positive), complete blood count and blood film, serum total bilirubin, and LDH. If evidence of hemolysis is found, testing could then also include unconjugated serum bilirubin and serum haptoglobin, as recommended by Talecris,[3] and curtailment of the course of IVIG should be considered. This would allow a rapid identification of patients at risk for RBC hemolysis after IVIG, and possible cessation of therapy, with special attention to female patients of non-O blood group receiving large cumulative dose of IVIG, who have evidence of an underlying inflammatory state.

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