Intravenous Immunoglobulin-induced Hemolysis

Divya M Radhakrishnan1, Niraj Kumar2, Ishita Desai3, Ashutosh Tiwari4, Mritunjai Kumar5, Sheetal Malhotra6, Gita Negi7

1Assistant Professor, Department of Neurology, All India Institute of Medical Sciences, Rishikesh, Uttarakhand; Department of Neurology, All India Institute of Medical Sciences, New Delhi, Delhi; 2Additional Professor; 3Senior Resident; 4Assistant Professor; 5Assistant Professor, Department of Neurology; 6Assistant Professor; 7Professor, Department of Transfusion Medicine, All India Institute of Medical Sciences, Rishikesh, Uttarakhand, India

Sir,

Intravenous immunoglobulin is an established treatment for many immune-mediated disorders and primary immune deficiency states. Hemolytic anemia (HA) is a known adverse effect in patients receiving IVIG for various therapeutic indications.1-3 The most speculated mechanism of hemolysis is a dose-dependent, passive transfer of anti-A/B hemagglutinins from IVIG product in non-O blood group individuals.4-6 There are many reports of HA occurring in patients of GBS and other neurological disorders after IVIG therapy.1-3,7-9 In this article, we report two cases of IVIG-induced hemolysis from the neurology department of our institute.

Case 1

A 67-year-old female, with no pertinent past medical history, presented with a 3-day history of acute onset progressive quadriparesis with intact bladder-bowel functions. Global areflexia on neurological examination with intact sensations along with nerve conduction studies (NCS) suggestive of motor, demyelinating polyneuropathy and albuminocytological dissociation in cerebrospinal fluid (CSF) examination led to the diagnosis of GBS. We administered IVIG at a dose of 0.4 gm/kg/day for 5 days. She received 170 gm of IVIG, considering a body weight (BW) of 85 kg. Although her limb weakness stabilized, she developed acute progression of anemia on day 9 of starting IVIG and her hemoglobin dropped to 8 gm/dL a day later (Fig. 1A). Her uncorrected reticulocyte count was 22% (normal value: <2.5%) and serum lactate dehydrogenase (LDH) level elevated to 670 (normal value: <240 units/L) on day 10 after initiating IVIG infusion, suggestive of intravascular hemolysis. Peripheral smear revealed 2–3 nucleated red blood cells (RBCs)/100 white blood cells and abundant polychromatophils. Her blood group was AB type Rhesus positive, but antibody screening identified clinically significant anti-A and anti-B antibodies. Her direct antiglobulin test (DAT) was negative on two occasions. She was transfused with one unit of packed 0 red blood cells. Her hemoglobin improved to 11.2 gm/dL and her reticulocyte count dropped to 2% on day 24 after IVIG initiation.

Case 2

A 28-year-old male, with no significant past medical history, presented with a 4-day history of acute onset progressive motor quadriparesis without bladder-bowel involvement. Neurological examination revealed global areflexia and intact sensations. Motor demyelinating polyneuropathy in NCS and albuminocytological dissociation in CSF examination favored the diagnosis of GBS. Considering his BW of 70 kg, we infused a total IVIG dose of 140 gm over 5 days. He developed acute onset anemia with a rapid drop in hemoglobin level to 7.7 gm/dL on day 10 of initiating IVIG (Fig. 1A). Rise in indirect bilirubin and serum LDH (Fig. 1C and 1D) along with peripheral smear showing nucleated RBCs and polychromatophils, favored hemolysis. His blood group was AB type Rhesus positive, and antibodies screening revealed clinically significant levels of anti-A and anti-B antibodies. Her direct antiglobulin test (DAT) was negative. He was conservatively managed and transfused two units of packed red blood cells. His hemoglobin improved to 11.8 gm/dL on day 24 after IVIG initiation.

Intravenous immunoglobulin products used in both cases were of the same lot; the liquid preparation had 5 gm of human immunoglobulin G and maltose as a stabilizer in 100 mL vial. Analysis of the IVIG products revealed high titer of anti-A [1024 (IgM) and
the binding of IgG on the RBCs, bringing it below the detection threshold. The current industry standard antibody titers are 1:64 for anti-A and 1:32 for anti-B; there should not be any agglutination beyond 1:64. Both cases reported here received the same liquid preparation of IVIG. The immunological analysis of IVIG product used in the patients with hemolysis revealed a higher anti-A and anti-B titer than the permissible limit. The adverse reactions were reported to the IVIG manufacturer, and the culprit batch was withdrawn from the market. None of the other patients who received IVIG during the same period had developed hemolysis. It is possible that the titers of anti-A and anti-B varied within the IVIG lot and patients with higher risks developed hemolysis. Individual susceptibility and certain unidentified patient factors might have also contributed to the occurrence of clinically significant hemolysis. Measures like immunoaffinity chromatography can observed the highest risk for hemolysis in patients with AB blood group, those who were first time recipients, those who were not on immunosuppressants, and who had a positive (≥1+) DAT immediate postinfusion. We observed clinically significant hemolysis in two patients who received IVIG for treatment of GBS. Both received IVIG for the first time, at a dose of 2 gm/kg BW and had AB type Rhesus positive blood group. The DAT in our patients may be false negative because of rapid removal of the sensitized RBCs. In severe hemolysis, RBCs are cleared so quickly, and in such great numbers, that there are few circulating sensitized RBCs left for detection. Most commercial antiglobulin tests screen for antibodies to IgG, complement C3, or both. Autoantibodies other than IgG, such as IgM or IgA can cause a false negative DAT. In our patients, high titers of IgM anti-A and anti-B antibodies compared to IgG in the IVIG product might have competitively inhibited the binding of IgG on the RBCs, bringing it below the detection threshold. The current industry standard antibody titers are 1:64 for anti-A and 1:32 for anti-B; there should not be any agglutination beyond 1:64. Both cases reported here received the same liquid preparation of IVIG. The immunological analysis of IVIG product used in the patients with hemolysis revealed a higher anti-A and anti-B titer than the permissible limit. The adverse reactions were reported to the IVIG manufacturer, and the culprit batch was withdrawn from the market. None of the other patients who received IVIG during the same period had developed hemolysis. It is possible that the titers of anti-A and anti-B varied within the IVIG lot and patients with higher risks developed hemolysis. Individual susceptibility and certain unidentified patient factors might have also contributed to the occurrence of clinically significant hemolysis. Measures like immunoaffinity chromatography can observed the highest risk for hemolysis in patients with AB blood group, those who were first time recipients, those who were not on immunosuppressants, and who had a positive (≥1+) DAT immediate postinfusion. We observed clinically significant hemolysis in two patients who received IVIG for treatment of GBS. Both received IVIG for the first time, at a dose of 2 gm/kg BW and had AB type Rhesus positive blood group. The DAT in our patients may be false negative because of rapid removal of the sensitized RBCs. In severe hemolysis, RBCs are cleared so quickly, and in such great numbers, that there are few circulating sensitized RBCs left for detection. Most commercial antiglobulin tests screen for antibodies to IgG, complement C3, or both. Autoantibodies other than IgG, such as IgM or IgA can cause a false negative DAT. In our patients, high titers of IgM anti-A and anti-B antibodies compared to IgG in the IVIG product might have competitively inhibited the binding of IgG on the RBCs, bringing it below the detection threshold. The current industry standard antibody titers are 1:64 for anti-A and 1:32 for anti-B; there should not be any agglutination beyond 1:64. Both cases reported here received the same liquid preparation of IVIG. The immunological analysis of IVIG product used in the patients with hemolysis revealed a higher anti-A and anti-B titer than the permissible limit. The adverse reactions were reported to the IVIG manufacturer, and the culprit batch was withdrawn from the market. None of the other patients who received IVIG during the same period had developed hemolysis. It is possible that the titers of anti-A and anti-B varied within the IVIG lot and patients with higher risks developed hemolysis. Individual susceptibility and certain unidentified patient factors might have also contributed to the occurrence of clinically significant hemolysis. Measures like immunoaffinity chromatography can
Correspondence

Correspondence

Journal of the Association of Physicians of India, Volume 70 Issue 10 (October 2022)

91

considerably reduce the incidence rate of IVIG-associated HA by decreasing the amount of anti-A/B isoagglutinins in the IVIG product. However, hemolytic reactions continue to occur and at times severe enough, requiring transfusion. Physicians should monitor high-risk patients for 5–10 days after IVIG infusion. If the patient has a drop in hemoglobin level, testing for markers of hemolysis, including DAT, is recommended.

Our article highlights a potentially serious but under-recognized side effect of IVIG therapy. It is important that medical practitioners are aware of this adverse effect for early recognition and management. A package insert containing an antibody titer of IVIG preparation is highly recommended.

ACKNOWLEDGMENT

The authors acknowledge Dr Aseem Kumar Tiwari and Mr Shubhasis Mitra for assisting in advanced immunohematological testing. The authors are also acknowledging their gratitude to the patients and their families.

PATIENT CONSENT

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

REFERENCES