CASE REPORT

# A Case Report of Intravenous Immunoglobulin (IVIG) Induced Haemolytic Anaemia

**Karan B Shah[1], Harsha D Makwana[2], Supriya D Malhotra[1], Pankaj R Patel[1]**

[1]Department of Pharmacology, Smt. NHL Municipal Medical College, Ahmedabad, Gujarat, India, [2]Department of Emergency Medicine, VS General Hospital, Ahmedabad, Gujarat, India

## ABSTRACT

A 30-year old female patient presented at emergency medicine department at our hospital with the chief complaints of severe body ache and weakness of bilateral upper and lower limbs. She was diagnosed to be suffering from inflammatory myositis based on her investigations by her treating physician. She received 0.4 g/kg Intravenous Immunoglobulin (IVIG) (Total 120 gm given) and 1 gm IV methyl prednisolone once a day over a period of five days. In the reports after 2 days of initiation of IVIG therapy the blood profile showed decrease in the haemoglobin levels and gradual increase in the total bilirubin levels. The patient was diagnosed with haemolytic anaemia due to IVIG by the consulting physician. The patient was transfused with 3 units of whole blood and started with oral prednisolone 1 mg/kg/day as a treatment of haemolytic anaemia. Gradually the haemoglobin level started to rise and went near the baseline level on 34th day of initiation of IVIG therapy. Haemolytic anaemia is a potentially serious and possibly under recognized side effect of IVIG therapy with the incidence of 0.1 to 1%. So, the clinician should be vigilant when the patient is given IVIG therapy and check the warning signs of haemolytic anaemia.

**Key words:** Adverse drug reaction, adverse effect, haemolytic anaemia, intravenous immunoglobulin

**Correspondence:**
Dr. Supriya D Malhotra,
Professor and Head, Department of Pharmacology, Smt. NHL Municipal Medical College, Ellis Bridge, Ahmedabad-380 006, Gujarat, India.
E-mail: supriyadmalhotra@gmail.com

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## INTRODUCTION

Intravenous Immunoglobulin's (IVIGs) are sterile, purified Immunoglobulin G (IgG) products manufactured from pooled human plasma and typically contain more than 95% unmodified IgG.[1] It is an immunomodulating agent that has multiple activities including modulation of complement activation; suppression of idiotypic antibodies; saturation of Fc receptors on macrophages; and suppression of various inflammatory mediators, including cytokines, chemokines, and metalloproteinases.[2] IVIG is used to treat various autoimmune, infectious, and idiopathic diseases. It is accepted for use in persons with Kawasaki disease, Guillain-Barre syndrome, and polymyositis/dermatomyositis.[3] Inflammatory myopathy (inflammatory muscle disease or myositis) is disease featuring weakness and inflammation of muscles and (in some types) muscle pain.[4,5] Multiple studies have shown IVIG is most effective in Polymyositis.[6] Common adverse reactions to treatment with IVIG include headache, renal insufficiency, hepatitis C, meningeal irritation, and thrombosis. Large doses of IVIG have been recognized as a cause of haemolytic anaemia, which occurs by means of passive transfusion; this rare complication has been given little attention.[4] In our patient haemolytic anaemia has been reported after IVIG therapy.

## CASE HISTORY

A 30-year old female patient presented at emergency medicine department at our hospital with the chief complaints of severe body ache and weakness of bilateral upper and lower limbs. On taking detailed history, the patient was relatively asymptomatic before two months when she developed generalized body pain. She took loose medications provided by the general practitioner and the symptoms alleviated. Again after a month she developed severe body pain and bilateral limb weakness. She was taken to a private hospital where she was investigated for Anti-Nuclear Antibodies and C-reactive proteins and tested positive for both. She was diagnosed to be suffering from inflammatory myositis based on her investigations by her treating physician. On checking the treatment given she had received 0.4 g/kg IVIG (Total 120 gm given) and 1 gm IV methyl prednisolone once a day over a period of five days but the symptoms did not respond to the treatment so she was transferred to our hospital. In the reports after 2 days of initiation of IVIG therapy the blood profile showed decrease in the haemoglobin levels and gradual increase in the total bilirubin levels. The patient also reported positive for direct coombs' test and the ferritin levels were too high. The patient was diagnosed with haemolytic anaemia due to IVIG by the consulting physician. The patient was transfused with 3 units of whole blood and started with oral prednisolone 1 mg/kg/day as a treatment of haemolytic anaemia. Gradually the haemoglobin level started to rise and went near the baseline level on 34th day of initiation of IVIG therapy. This adverse drug reaction was reported to the nearest ADR Monitoring Centre and was uploaded to the Vigiflow with the report id 2017-03646.

## DISCUSSION

Significant number of IVIG-associated serious adverse events affecting hematologic systems have been reported.[7] The incidence of haemolytic anaemia caused by intravenous immunoglobulin therapy is between 0.1 to 1.0%.[8] Serious and sometimes fatal complications of intravascular haemolysis including anaemia, acute renal insufficiency, or disseminated intravascular coagulation have been rarely reported.[7] Haemolytic anaemia is a potentially serious and possibly under recognized side effect of IVIG therapy [Figures 1 and 2; Table 1]. The aetiology of clinically significant haemolysis in patients treated with IVIG is multifactorial. Isohemagglutinins (anti-A/B antibodies) present in IVIG can cause direct antibody attack on RBCs.[9] Factors that may increase the risk for haemolysis include the dose of IVIG, the titre of the isohemagglutinin antibody in the IVIG preparation, the strength of the patient's antigen expression, the affinity of the antibody for the antigen, or a combination of these factors. The usual dose of IVIG ranges from 0.4-4 g/Kg. It is known that haemolytic anaemia can



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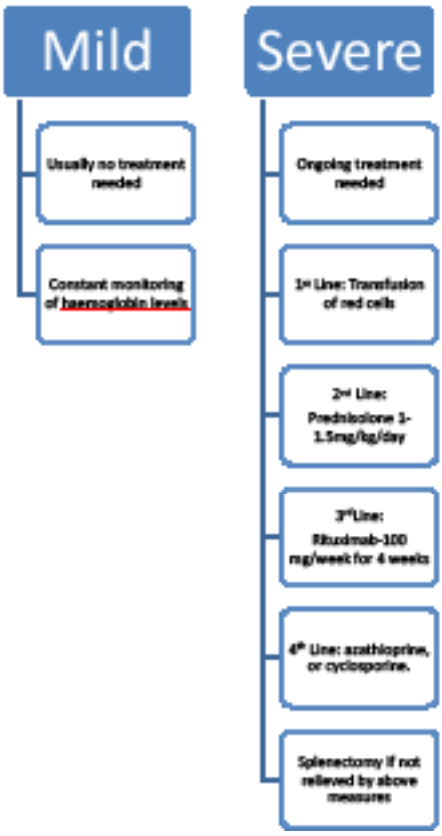


**Figure 1:** Treatment guidelines for haemolytic anaemia

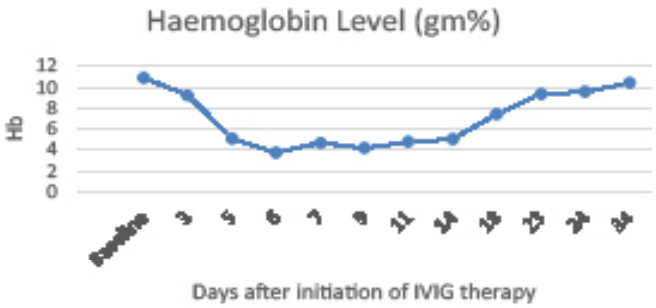


**Figure 2:** IVIG induced haemolytic anaemia as depicted

**Table 1:** Haemoglobin and Total bilirubin levels corresponding to day from the start of IVIG therapy

| Days after initiation of IVIG therapy | Haemoglobin Level (gm%) | Total Bilirubin Level (biliT) mg/dL |
|---|---|---|
| Baseline | 10.9 | 0.79 |
| 3 | 9.25 | 2.33 |
| 5 | 5.10 | 4.53 |
| 6 | 3.75 | |
| 7 | 4.70 | 2.72 |
| 9 | 4.19 | 1.85 |
| 11 | 4.79 | 1.70 |
| 14 | 5.05 | 1.02 |
| 18 | 7.44 | |
| 23 | 9.34 | |
| 24 | 9.57 | |
| 34 | 10.4 | 0.46 |

occur even with doses as low as 1 g/kg.[10] Our patient received only 0.4 g/kg and yet developed haemolytic anaemia. Our patient had AB positive blood group and it is documented that there is greater risk for haemolysis in patients with non-O blood groups.[10] It is hypothesized that patients with non-O blood groups, with low concentrations (congenital or acquired) of soluble A and/or B substance in their plasma, are at increased risk for haemolysis due to their inability to neutralize the anti-A and/or anti-B isohemagglutinins present in the plasma after IVIG infusion.[11] Another possible mechanism for a decrease in haemoglobin with IVIG, independent of isoantibodies, is enhanced erythrocyte sequestration. Since IVIG contains high molecular weight IgG complexes, these can mimic immune complexes by activating complement. These complexes bind to complement receptor 1 on RBCs which leads to erythrophagocytosis and hence a reduction in haemoglobin. Predictors for this phenomenon include age and RBC ability to bind the IVIG immune complex-like moieties.[12] Haemolytic anaemia should be considered in patients treated with IVIG who experience a drop in haemoglobin following treatment and/or who develop clinical signs of haemolysis. It is important that physicians are aware of this potential complication for early recognition as well as for disclosing this potential side effect to patients and their families. It should be a routine practice to monitor the haemoglobin 24 to 48 h after completion of IVIG and one week after discharge, particularly if retreatment is necessary. A work up for haemolysis is not routinely required except if this complication is suspected. Further insight is still required in regards to the pathogenesis and predisposing factors for haemolysis in this patient population.[13] People who have mild haemolytic anaemia may not need treatment, as long as the condition doesn't worsen. People who have severe haemolytic anaemia usually need on-going treatment. Treatments for haemolytic anaemia include blood transfusions, medicines, plasmapheresis, surgery, blood and marrow stem cell transplants, and lifestyle changes. Haemolytic anaemia is a severe condition and it can be caused by various medications which include cephalosporin's (most common cause), dapsone, levodopa, levofloxacin, methyldopa, nitrofurantoin, non-steroidal anti-inflammatory drugs (NSAIDS), penicillin and its derivatives and many more.[14] So, the clinician should be vigilant when the patient is given IVIG therapy and check the warning signs of haemolytic anaemia.

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