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Association of hemolysis with high dose intravenous immunoglobulin therapy in pediatric patients: An open-label prospective trial☆

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ABSTRACT

Immunoglobulin therapy can be used to treat a wide variety of diseases. However, intravenous immunoglobin products can cause several adverse reactions, including hemolysis. The objective of this study was to determine the extent of anemia and hemolysis after high dose intravenous immunoglobin (2 g/kg) and its relationship to the ABO blood type system and hemolytic anemia blood parameters in pediatric patients.

Incidence of 'Intravenous immunoglobulin related hemolysis' was %19 (6/31) after high dose intravenous immunoglobulin therapy. The blood parameters were measured before IVIG infusion (1–24 h before infusion) and 3–10 days after the first day of infusion. In terms of decrease in Hb levels; decline of <1 g/dL was detected in 25 patients (80.6%), ≥1 g/dL in 2 patients (6.5%) and >2 g/dL (severe hemolysis) in 4 patients (12.9%) after infusion. The decrease in hemoglobin, haptoglobin levels, the increase of reticulocyte count or direct bilirubin were statistically significant after infusion. Five of 6 hemolysis patients had non-O blood group, however statistically significant difference was not noted between these two groups. Also, intravenous immunoglobulin-related hemolysis was determined significantly higher in female than male patients.

Conclusion: Mild to moderate hemolysis may be undetected after infusion and the true incidence of such reactions is difficult to document without careful clinical and laboratory follow-up. A careful risk assessment analysis should be performed before intravenous immunoglobulin infusion.

1. Introduction

Immune-globulins are antibody-containing products purified from large pools (e.g., >10,000 L) of human plasma using techniques that separate the immunoglobulin fraction from other proteins and plasma constituents. Intravenous immune-globulin (IVIG) have a multitude of effects on the immune system including modulation of the expression and function of Fc receptors, interference with the activation of complement and the cytokine network and provision of anti-idiotypic antibodies [1,2]. IVIG, first introduced for the treatment of primary immune deficiencies, is currently used in a wide range of other disorders [3,4]. IVIG is used at a 'replacement dose' of 200–400 mg/kg body weight, given approximately once in 3 weeks. In contrast, 'high-dose' IVIG given most frequently at 2 g/kg is used as an 'immunomodulatory' agent in an increasing number of immune and inflammatory disorders [3,5]. Cases of unexpected side affects encountered related to higher doses of IVIG treatment have been reported [6–8].

Immediate or delayed adverse events (AEs) following IVIG infusions in children were reported 10.3% and 41.4%, respectively [9]. Common side effects of IVIG infusion include pyrexia, rigors and headache. Rare, but significant adverse events include acute kidney

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injury related to sucrose induced osmotic nephropathy, hypersensitivity reactions, vascular thrombosis and hemolysis. The majority of adverse reactions to IVIG were mild and transient [6].

IVIG administration may result in clinically significant hemolysis. IVIG-related hemolysis (IRH) became a spotlight and controversial topic recently. The hemolysis is usually self-limited with rapid resolution, but may be of significant clinical concern with occasional patients requiring red blood cell transfusion [6,10]. The IVIG Hemolysis Pharmacovigilance Group of Canada has formalized the definition of IRH with inclusion and exclusion criteria [11]. A case was considered as IRH reactions when hemolysis occurred within 10 days of IVIG administration and when the following additional criteria were met: decrease of than 1 g/dL in hemoglobulin (Hb) and a positive direct antiglobulin test (DAT) and at least one of the following findings: (1) increased reticulocyte (Ret) count, (2) increased lactate dehydrogenase (LDH), (3) low haptoglobulin, (4) unconjugated hyperbilirubinemia, or (5) elevated free Hb in plasma. IRH reactions were considered severe in case of a Hb decline of greater than 2 g/dL or need for red blood cell (RBC) transfusion. The European Pharmacopeia recommends that anti-A or anti-B hemagglutinins should be bellow detectable level at the 1:64 dilution of IVIG preparations [12]. The World Health Organization (WHO) has reference reagents to standardize the hemagglutination testing for anti-A and anti-B in IVIG [13]. Clinically significant IRH may occasionally occur at titers of anti-A and anti-B hemagglutinins lower than 1:64 in IVIG preparations.

Several recent publications reported the occurrence of IRH in adults and proposed hypotheses on the etiology of this event [8,14–17]. There are few prospective studies of the prevalence of AEs in pediatric patients [9]. As far as we know, IRH reactions were not documented with laboratory findings in these pediatric studies. So this is the first prospective designed study in children that determines the extent of anemia and hemolysis after high dose intravenous immunoglobin (2 g/kg) and its relationship to the ABO blood type system, gender and hemolytic anemia blood parameters (Direct antiglobulin test, reticulocyte count, lactate dehydrogenase, haptoglobulin, conjugated/unconjugated bilirubin) in pediatric patients.

2. Materials and methods

The study was designed as an open-label, prospective, observational study. Patients were recruited from the pediatric services at Ankara Children's Hematology and Oncology Training Hospital during the period from 1 June 2014 to 1 June 2015. The children between 2 and 18 years old age were included in the study. They received IVIG therapy (total dose 2 g/kg) for the treatment of neurological, rheumatologic and cutaneous drug reaction diseases. Children with the history of blood transfusion and with clinical signs of anemia and and/or infection were excluded from the study. The study was approved by the 'Ethical Review Board' of Ankara Children's Hematology and Oncology Training Hospital.

The following parameters were evaluated before IVIG infusion (1–24 h before infusion) and 3–10 days after the first day of infusion: blood hemoglobin (Hb), plasma haptoglobin (H), blood reticulocytes (Ret%), plasma lactate dehydrogenase (LDH), plasma total and indirect bilirubin (T.Bil and D.Bil.), DAT. The plasma haptoglobin levels were also measured 24 h after the first day of IVIG infusion. Hb (g/dL) measurements were carried out with Beckman Coulter LH 780 device with photometric method. T.Bil, D.Bil measurements were carried out with Beckman Coulter AU 680 device with colorimetric method and LDH with enzymatic method. Collected serum samples of haptoglobin (H) were stored at −80 °C temperature. Serum H level was determined by an immunological (nephelometric) method using Beckman Coulter Immage 800 device. The normal range of H is 41–165 mg/dL. The criteria for the judgment of DAT is as follows; ++++, one solid clot; +++, several large clots; ++, medium-sized clots and clear background; +, small clots and turbid background; −, no hemagglutination or hemolysis. The reference range of the reticulocyte percentage is 0.5–1.5%. The individual blood types were determined according to the ABO blood type classification.

Table 1
All indications (reported in more than one subject).

Indications (n = 31, Female/Male 11/20)	Number of cases (n)
Gullain-Barré syndrome (GBS)	8
Chronic inflammatory demyelinating polyneuropathy	4
Kawasaki disease	3
Dermatomyositis polymyositis	2
Limbic encephalitis	2
Myocarditis	7
Transverse myelitis	1
Bulbar myelitis	1
Henoch-Schönlein purpura with intussusception	1
Miller Fischer syndrome	1
Steven–Johnson syndrome	1

We accepted the IRH criteria outlined by 'The Canadian IVIG Hemolysis Pharmacovigilance Group'. Hb decline of more than 2 g/dL or in need of RBC transfusion were considered severe hemolytic reactions. All patients were treated with the same IVIG product (GENIVIG Sichuan Yuanda Shuyang Pharmaceutical Co., Ltd., China). Test results of anti-A and anti-B in the IVIG product are generally in "≤1:16–1:32", and most of the batches were "≤1:16".

2.1. Statistical analyses

Analyses of data was done with 'Statistical Package for the Social Sciences (SPSS) for Windows 11.5. For analyzing data, descriptive statistics including frequency, percentage, mean ± standard deviation, median (min–max.) were used. Statistical analysis including Cox proportional hazard model, the t-test (for the analysis of quantitative variables between the two groups) and Pearson chi-square test and Fisher exact (for the relationship between qualitative variables) were used.

Quantitative variables were compared between the baseline and follow-up using a paired t-test (if normally distributed) or the Wilcoxon signed-rank test (if not normally distributed). The Friedman test was used when the same parameter measured under different conditions on the same subjects. Dichotomous variables were compared using McNemar's test. $p < 0.05$ was considered as significant.

3. Results

Thirty-one patients (20 male, 11 female) were evaluated after high dose IVIG infusion. The mean age of the patients was 8.75 ± 5.23 year (2–18 year). Six patients were given repeated IVIG therapy with the diagnosis chronic inflammatory demyelinating polyneuropathy (CIDP) and dermatomyositis/polymyositis. Each patient was given IVIG with the total dose 2 g/kg during the first to fifth days [Median 4.64 day (1–5 days)]. The number and the diagnosis of patients treated with IVIG therapy in our 'General Pediatric Clinic' were shown in Table 1.

All patients receiving IVIG treatment presented a significant decrease in Hb after IVIG infusion ($p < 0.05$). The decrease in Hb was followed by a significant increase in D.Bil ($p < 0.05$), an increase in RET ($p < 0.05$) and insignificant increase in LDH and in T.Bil ($p > 0.05$) (Table 2). DAT was positive after IVIG infusion in 11 of 31 patients. 5 of 11 patients with DAT positivity after IVIG were not provided the IRH criteria. Plasma haptoglobin levels were measured three