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Use of intravenous immunoglobulin in neonates with haemolytic disease and immune thrombocytopenia

Primena intravenskih imunoglobulina kod novorođenčadi sa hemoliznom bolesti i imunskom trombocitopenijom

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Abstract

Background/Aim. Intravenous immunoglobulin is a blood product made of human polyclonal immunoglobulin G. The mode of action of intravenous immunoglobulin is very complex. It is indicated in treatment of neonatal immune thrombocytopenia and haemolytic disease of the newborn. The aim of the study was to present our experience in the use of intravenous immunoglobulin in a group of term neonates. **Methods.** We analysed all relevant clinical and laboratory data of 23 neonates who recieved intravenous immunoglobulin during their hospitalization in Neonatal Intensive Care Unit of Mother and Child Health Care Institute over a five year period, from 2006. to 2010. **Results.** There were 11 patients with haemolytic disease of the newborn and 12 neonates with immune thrombocytopenia. All of them recieved 1–2 g/kg intravenous immunoglobulin in the course of their treatment. There was no adverse effects of intravenous immunoglobulin use. The use of intravenous immunoglobulin led to an increase in platelet number in thrombocytopenic patients, whereas in those with haemolytic disease serum bilirubin level decreased significantly, so that some patients whose bilirubin level was very close to the exchange transfusion criterion, avoided this procedure. **Conclusion.** The use of intravenous immunoglobulin was shown to be an effective treatment in reducing the need for exchange transfusion, duration of phototherapy and the length of hospital stay in neonates with haemolytic disease. When used in treatment of neonatal immune thrombocytopenia, it leads to an increase in the platelet number, thus decreasing the risk of serious complications of thrombocytopenia.

Key words:
thrombocytopenia, neonatal alloimmune; anemia, hemolytic; infant, newborn; immunoglobulins, intravenous.

Apstrakt

Uvod/Cilj. Intravenski imunoglobulini su preparat humanih imunoglobulina G dobijenih iz plazme zdravih davalaca. Mehanizam delovanja intravenskih imunoglobulina veoma je složen. Njihova primena je indikovana u lečenju hemolizne bolesti i imunskoj trombocitopeniji novorođenčeta. Cilj rada bio je prikaz sopstvenog iskustva u primeni intravenskih imunoglobulina u grupi terminske novorođenčadi. **Metode.** Analizirani su anamnestički podaci, klinički nalazi i laboratorijski rezultati 23 novorođenčeta koji su u periodu od 2006. do 2010. dobijali intravenske imunoglobuline tokom hospitalizacije u neonatalnoj intenzivnoj nezi Instituta za majku i dete Srbije „Dr Vukan Čupić". **Rezultati.** Kod 11 novorođenčadi indikacija za primenu intravenskih imunoglobulina bila je hemolizna bolest novorođenčeta, dok je 12 novorođenčadi imalo imunsku trombocitopeniju. Kod svih bolesnika primenjena je doza od 1 do 2 g/kg telesne mase intravenskih imunoglobulina. Nisu registrovane komplikacije primenjene terapije. Kod novorođenčadi sa hemoliznom bolešću došlo je do znatnog sniženja nivoa bilirubina, što je omogućilo da najveći broj bolesnika izbegne eksangvinotransfuziju. Primena intravenskih imunoglobulina dovela je do značajnog porasta broja trombocita kod bolesnika sa imunskom trombocitopenijom. **Zaključak.** Primena intravenskih imunoglobulina vrlo je efikasna za snižavanje potrebe za eksagvinotransfuzijom, za skraćenje trajanja fototerapije i skraćenju trajanja hospitalizacije kod novorođenčadi sa hemoliznom bolešću. Kod novorođenčadi sa imunskom trombocitopenijom primena intravenskih imunoglobulina dovodi do značajnog porasta broja trombocita, snižavajući time rizik od potencijalno ozbiljnih komplikacija trombocitopenije.

Ključne reči:
trombocitomenija, neonatalna, aloimunska; anemija, hemolitička; novorođenče; imunoglobulini, intravenski.

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Introduction

Intravenous immunoglobulin (IVIG) is a blood product made of human polyclonal immunoglobulin G (IgG). It is obtained from plasma of thousands of healthy blood donors, therefore providing a great variety of antibodies. It contains more than 95% of unmodified immunoglobulin G and some traces of immunoglobulin A and immunoglobulin M. It has been first used in treatment of primary immunodeficiency and nowadays is used in treatment of many hematological, neurological, rheumatic and dermatological diseases [1]. The mode of action of immunoglobulin is complex and it includes modulation of Fc-receptor mediated phagocytosis, complement binding and prevention of membrane attack complex formation, inhibition of some cytokines, down-regulation of antibody production etc. [1, 2]. According to well-established recommendations, the indications for use of IVIG in neonates are: haemolytic disease of the newborn (HDN), immune thrombocytopenia and fetal hydrops caused by PARVO B19 virus [3]. The use of IVIG in prevention and treatment of neonatal sepsis, especially in preterm neonates, is still controversial [4, 5].

The aim of this study was to present our experience in the use of IVIG in a group of term neonates.

To our knowledge, this is the first presentation of national experience in the use of IVIG in neonates with hemolytic disease of the newborn and neonates with immune thrombocytopenia.

Methods

Over a five year period, from 2006 to 2010, intravenous immunoglobulin was administered in the Neonatal Intensive Care Unit (NICU) of Mother and Child Health Care Institute of Serbia "Dr. Vukan Čupić" in the treatment of 23 term neonates. This presentation encompasses two groups of patients: neonates with haemolytic disease of the newborn and neonates with immune thrombocytopenia. All the data concerning pregnancy, perinatal history, management in immediate postnatal period as well the treatment received prior to admission to the NICU, were collected from medical records. We obtained written consent from the parents for blood sample collection of the neonates.

The group I of patients included of neonates with isoimmune haemolytic disease (HD) due to Rh or ABO incompatibility between the blood group of the mother and the newborn, proven by the positive direct Coombs test, indirect hypebilirubinemia and increased reticulocyte count. Hyperbilirubinemia was considered significant if phototherapy and/or exchange transfusion (ET) was required [6]. Laboratory investigations included: serum bilirubin level (total and direct), direct Coombs test, full blood count with reticulocyte count. Each neonate was treated with continuous intensive phototherapy. All neonates received 1–2 g/kg body weight of IVIG in intravenous infusion, over no less than 6 hours. Estimation of serum bilirubin was done 6 hours after termination of IVIG infusion and every 12 hours in the next two days.

The group II of patients included neonates with immune thrombocytopenia. Laboratory investigations included: full blood count, standard biochemical analyses, sepsis workup with determination of C-reactive protein. Abdominal and cranial ultrasonography was performed in each patient. Indication for platelet transfusion was platelet count of less than 20×10^9/L. All the patients in this group received 1–2 g/kg body weight of IVIG in intravenous infusion. Platelet count was repeated 12 and 24 hours after IVIG infusion, and later during hospitalization as needed, according to the latest platelet number. Platelet antigen typization could not be done since it is not available in our country.

Results

During a 5-year period, 23 neonates received IVIG during their hospitalization in the NICU. Haemolytic disease of the newborn was an indication for IVIG treatment in 11 (47.8%) patients, while 12 (52.2%) patients had immune thrombocytopenia.

In the group of patients with haemolytic disease, 7 (63.6%) patients had OA incompatibility, two (18.2%) OB incompatibility and two (18.2%) patients had Rh incompatibility. The average age on admission was 1.2 days. All the patients had received phototherapy and one patient had had ET prior to admission to our NICU. All the neonates had normal physical examination apart from jaundice. Bilirubin level on admission ranged from 218 to 347 μmol/L. All the patients received IVIG (dose 1–2 g/kg body weight), with no side effects noted. They were all receiving intensive phototherapy concomitantly. The average duration of phototherapy was 40 hours. Two patients needed ET according to their bilirubin level on admission. When plotted on nomogram for prediction of risk for exaggerated jaundice [6], all our patients were in high risk zone on admission. Twenty-four hours after IVIG infusion 8 (72.8%) of them were in low intermediate risk zone, while 2 (18.2%) of them were in high intermediate risk zone and one (9.0%) patient was in low risk zone, as shown in Figure 1. Four (33.3%) of the patients received red blood cell transfusion because of severe anemia. The average length of hospitalization in this group of patients was 9.0 days.

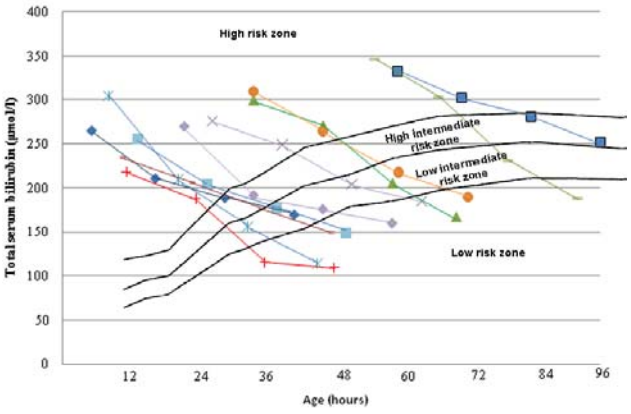

Fig. 1 – Bilirubin level trend in neonates with haemolytic disease.

In the group of patients with immune thrombocytopenia, two (16.7%) neonates were born to mothers with thrombocytopenia due to immune thrombocytopenic purpura (ITP), whereas 10 (83.3%) patients were born to mothers with normal platelet count. The average age in this group of patients was 1.8 days. The platelet count on admission ranged from 7 to 45 × 10^9/L, with an average being 20.6 × 10^9/L. All the patients had normal physical examination apart from 8 (66.6%) patients in whom petechiae and/or ecchymoses were noted. Abdominal and cranial ultrasonography performed in each patient showed no signs of bleeding. All patients were treated with 1g/kg body weight of IVIG for up to two consecutive days, depending on the response in platelet count. The administration of IVIG was not associated with any complications. Three of the patients (25,0%) were put on corticosteroid treatment for prolonged thrombocytopenia, which did not resolve after IVIG administration. The average length of hospitalization was 13.3 days. The average period until the platelet count reached ≥ 100 × 10^9/L was 2, 4 days. All patients had normal platelet count on their discharge from hospital, with an average platelet count of 166.9 × 10^9/L.

Discussion

Intravenous immunoglobulin has been successfully used in treatment of isoimmune haemolytic anemia. Isoimmune haemolytic anemia of the newborn is a cause of neonatal hyperbilirubinemia due to haemolysis of fetal red blood cells, caused by transplacentally transmitted maternal antibodies active against antigens present on fetal erythocytes. It leads to an increased risk of bilirubin encephalopathy and kernicterus. The therapy is aimed at lowering the serum concentration of bilirubin or keeping it from further increase, so avoiding the levels at which kernicterus may occur. Neonatal isoimmune haemolytic disease is conventionally treated by phototherapy and ET [6]. The exact mechanism of action of IVIG in HDN is still not precisely explained. Intravenous immunoglobulin is believed to occupy the Fc receptors of reticuloendothelial cells and prevent further lysis of antibody-coated erythrocytes. It is found to decrease hemolysis leading to reduction in serum bilirubin level [7–12]. There is subsequently an important decrease in need for exchange transfusion [6, 7, 9].

Due to widely used preventive administration of anti-D prophylaxis in Rhesus-negative women, there is a decrease in Rhesus sensitization and subsequent haemolytic disease of the newborn. That is why a high proportion of haemolytic disease of newborn is nowadays caused by antibodies to other red blood cell antigens (anti-A, anti-B etc.) [7]. In our group of patients with haemolytic disease, Rh incompatibility was the cause of haemolysis in only two (18.2%) patients, whereas the major cause was OA incompatibility (63.6%).

Many studies have shown that the use of IVIG leads to a significant reduction in the need for ET [8–15]. Our data also confirmed that administration of IVIG reduced bilirubin level, decreasing it beneath the threshold for ET in 8 (66.6%) patients. Twenty-four hours following IVIG infusion an important decrease in bilirubin level was observed in most of our patients (72.8%), diminishing their risk from high to low intermediate. An infant whose bilirubin level is in low intermediate or low risk zone is at a very low risk to develop severe hyperbilirubinemia [6]. This result goes along with results of many authors who showed a significant reduction in bilirubin level after IVIG use [8–11]. Early administration of IVIG as soon as the diagnosis of haemolytic anemia is made is therefore recommended by many authors [8–11, 13]. Monpoux et al. [11] suggest that after an initial period of 4 hours of intensive phototherapy, IVIG might be used even in jaundice with negative Coombs test, mostly caused by ABO incompatibility.

The average duration of phototherapy in our patients was 40 hours and the average length of hospitalization was 9.0 days. Although we did not have a control group, the average length of hospitalization in our HD group is similar to that of HD group presented by Voto et al. [16]. In a systemic review by Gottstein and Coone [8], a reduction in the duration of phototherapy and hospital stay, when IVIG is used along with phototherapy for haemolytic disease, is emphasized. However, there is a great heterogeneity between the studies [8]. Shortened hospitalization and duration of phototherapy make a financial benefit which exceeds the cost of IVIG. It is considered to be a relatively safe product with rarely seen serious side effects [7–9, 13]. We did not note any immediate adverse effects either.

It is postulated that there is an icreased rate of late transfusions required in patients treated with IVIG for HDN 8. It is probably secondary to further haemolysis after the effect of IVIG has expired, so the Fc sites on reticuloendothelial cells become free again to bind antibody sensitized neonatal erythrocytes [7, 8, 11, 13]. One of the drawbacks of our analysis might be the lack of data showing the incidence of late transfusion rate in HDN group of patients.

Although we realize that the absolute number of our HDN group is limited, one may notice that our results do not differ from those of other similar studies [9, 13].

There are two types of neonatal immune thrombocytopenia. Neonatal autoimmune thrombocytopenia is secondary to transplacental passage of maternal platelet autoantibodies. It can be seen in neonates born to mother with autoimune disease, most commonly idiopathic thrombocytopenic purpura (ITP) or systemic lupus eritematodes (SLE). Neonatal alloimmune thrombocytopenia (NAIT) is caused by maternal alloimmunisation against fetal platelet antigens inherited from the father but absent on mother's platelets. Maternal anti-platelet antibodies then cross the placenta and destroy fetal platelets. The majority of casese are caused by antibodies against Human Platelet Antigen 1a – HPA-1a [17, 18]. The greatest risk of severe thrombocytopenia is intracranial haemorrhage (ICH), which may cause death or lead to neurological sequelae. Treatment of a neonate with NAIT is aimed at preventing or stoping thrombocytopenic bleeding [19, 20]. The first therapeutic choise is platelet transfusion [21]. It is often combined with IVIG, whose administration is associated with an increase in platelet count, after a period of 24–48h [22].

In our group of patients with thrombocytopenia, neonatal autoimmune thrombocytopenia was present in 2 (16.7%) patients. It is known that about 10% of neonates of mothers affected with some autoimmune disease, mostly ITP and SLE, develop thrombocytopenia [19]. It is a less common cause of thrombocytopenia than NAIT, as is shown in our group of patients. Neonatal autoimmune thrombocytopenia is usually mild. Both of our patients had severe thrombocytopenia ($\leq 20 \times 10^9$/L), which is uncommon, but they had no signs of visceral bleeding and recovered their platelet count after IVIG administration.

Fetomaternal incompatibility for HPA-1a causes about 75% of all cases of NAIT [21, 23–26]. It is typically diagnosed in an otherwise well neonate, who develops petechiae and/or purpura shortly after birth. Thrombocytopenia may also be noted when a full blood count is checked for sepsis workup or some other clinical reasons [17]. In our group of patients, 8 (66.6%) of them had petechiae and/or purpura with otherwise normal physical examination. When there is no possibility to screen blood of the mother and the father, which is the case in our country, it is of great importance to exclude other possible causes of thrombocytopenia (TORCH screening, "blueberry muffin" rash, intrauterine growth restriction, thrombosis, sepsis, etc). The testing to confirm NAIT would be performed in order to discover an antibody in the mother's plasma directed against a platelet-specific antigen present in the father, but not in the mother. This is a complex testing which should be done only in a laboratory with experience in this field [17].

If a neonate has low platelet count with no other explanation, so the clinical diagnosis of NAIT is confirmed, the first therapeutic choice in a bleeding newborn would be a random donor platelet transfusion if the platelet count is less than 30×10^9/L [18, 21]. Platelet number which presents an indication for transfusion slightly differs according to the literature source [20]. Neonates with no signs of bleeding and platelet count of more than 30×10^9/L should be closely monitored (including repeated platelet count and ultrasound examination). Many authors believe that in case of severe thrombocytopenia, the best treatment modality would be to give random donor platelet transfusion first and then to infuse IVIG and closely follow the platelet count [17, 20–22]. This is also the strategy accepted by our team. After transfusion of platelets, when it was indicated, all neonates in our presentation were infused with IVIG, which was not associated with any side effects.

Although there is no strong evidence to support the use of corticosteroids in the treatment of NAIT, some authors propose the use of methylprednisolone for neonates with prolonged thrombocytopenia if it persists after IVIG treatment [17]. Three (25%) of our patients were put on a short course of corticosteroids until their platelet count reached normal range.

Conclusion

Indications for the use of IVIG in neonates in our group of patients were haemolytic disease and immune thrombocytopenia of the newborn. Its use in addition to phototherapy in treatment of haemolytic disease of the newborn led to the reduction in the degree of haemolysis and therefore the need for exchange transfusion. It was also shown to be effective in increasing the platelet count in case of immune thrombocytopenia of the newborn. No side effects of IVIG were noted, so it can be considered a safe treatment for the newborn.

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