Brief Reports

Multiple Dose IVIG Treatment in Neonatal Immune Hemolytic Jaundice

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Summary

Isoimmune hemolytic jaundice due to ABO and Rh blood group incompatibility is an important problem in the neonatal period. Intravenous immune globulin (IVIG) treatment in isoimmune jaundice has been shown to be effective, but the response to treatment is variable. In this study, the effect of multiple doses IVIG therapy versus single dose IVIG therapy was investigated in 61 babies who had ABO and Rh hemolytic disease. Patients were divided into three groups. Group I received multiple dose IVIG treatment, group II received single dose IVIG treatment, and group III was not given any IVIG. All three groups received phototherapy. No exchange transfusion was needed in group I. The rate of exchange transfusion was 12 per cent in group II and 33 per cent in group III. Duration of phototherapy was shorter in group I than in groups II and III. It was concluded that IVIG treatment reduces the need of exchange transfusion in neonatal isoimmune hemolytic jaundice by lowering hemolysis. Multiple doses IVIG treatment appears to be better at blocking ongoing hemolysis.

Introduction

Hemolytic jaundice caused by blood group incompatibility has significant morbidity and mortality in the neonatal period.[1] It is accepted that introduction of anti-D for prophylaxis of Rh incompatibility reduces the number of cases with hemolysis. However, because the prophylactic anti-D treatment cannot often be given on time or in adequate dosage, Rh hemolytic disease remains an important problem of neonates, especially in developing countries like Turkey.[2] Furthermore, there is no prophylactic treatment for ABO and Rh subgroup incompatibilities. The conventional therapies for this disease are phototherapy, hydration and exchange transfusion. Recently, high dosage of intravenous immune globulin (IVIG) therapy has been shown to be effective in the treatment of isoimmune neonatal hemolytic disease.[2–8] IVIG treatment reduces the need of exchange tranfusion, duration of hospitalization, and phototherapy.[3,6,8,9]

IVIG has been used successfully in the treatment of autoimmune diseases.[10] It is suggested that in isoimmune hemolytic disease, IVIG prevents the destruction of sensitized erythrocytes in the reticulo endothelial system (RES) through binding of the Fc receptors.[6] Although this treatment is successful in isoimmune hemolytic disease, the response to IVIG varies and sometimes high blood bilirubin is not brought down to the desired level. With IVIG treatment, different exchange transfusion rates were found, from 6 to 20.5 per cent. Such differences might be due to the severity of hemolysis. The degree of hemolysis depends on the severity of immunization.[9,11] In other words, it will depend on the level of antibodies that cross from the mother to the baby through the placenta. We propose that if the level of isoantibodies is high, one dose of IVIG cannot be sufficient to stop ongoing hemolysis, and additional doses of IVIG may be needed. Thus, multiple doses of IVIG might overcome high antibody levels.

The effect of multiple doses of IVIG therapy could decrease the severity of hemolysis and hyperbilirubinemia in newborns. In this study, the effect of multiple doses of IVIG treatment versus single dose IVIG treatment was investigated in newborns who had blood group incompatibility.

Patients and Methods

Sixty-one full term babies with blood group incompatibility that were referred to our neonatal care unit between January 1996 and November 1998 were recruited for this study. The criteria for inclusion were as follows: the positivity of direct Coombs' testing of infants; ABO, Rh or subgroup incompatibility between mother and baby; no contributing risk factors (such as sepsis, or drug use by mothers) that

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TABLE 1
Serum bilirubin level (mg/dl) as criterion for exchange transfusion[12]

	Birth weight (g)				
	<1250	1250–1499	1500–1999	2000–2499	>2500
Standard risk	13	15	17	18	20
High risk	10	13	15	17	18

could raise bilirubin levels; no prematurity; bilirubin levels below the exchange transfusion criterion on admission. The cases were adequately hydrated and received phototherapy. Phototherapy was performed using a white quartz halogen lamp (Air Shields Microlite Phototherapy system), with a distance between the infant and light source of 41 cm. Phototherapy was started once the patient was admitted to the clinic. Bilirubin levels were measured every 4–6 h. Depending on the patient's condition, phototherapy was terminated when the bilirubin level decreased to the safe limit. After the cessation of phototherapy, patients were closely observed for at least one more day. Exchange transfusion was performed when bilirubin levels exceeded the accepted limits, which are shown in Table 1.[12]

Patients who were diagnosed with isoimmune hemolytic hyperbilirubinemia and fulfilled the above criteria were divided into three groups by order of admission. The order for grouping was not changed for any reason.

In their groups, the patients received IVIG 500 mg/kg body weight within 2–4 h of admission. Group I received one dose, and group II received three doses during 3 consecutive days. Approval was obtained from the parents and the local ethical committee.

The blood groups of mothers and babies were recorded. Hemogram, reticulocyte count and bilirubin levels of infants were analysed. The patients were monitored for possible side-effects.

The results were analysed by using analysis of variance (ANOVA), Tukey (post hoc) and chi-squared tests. $p < 0.05$ was considered as significant and the values were given as mean ± SD.

Results

A total of 61 infants, 34 males and 27 females, were included in the study. The mean age of the cases was 2.2 ± 1.2 days (between 0 and 7 days). In group I, 20 infants received multiple doses IVIG treatment; in group II, 20 infants received single dose IVIG treatment. All infants were given appropriate hydration and phototherapy.

When analysed according to blood group incompatibility, 34 out of the 61 cases (55.7 per cent) had ABO blood group incompatibility, 18 had Rh (D) incompatibility, two had Rh subgroup incompatibility and seven (11.5 per cent) had more than one (ABO + Rh) incompatibility (Table 2). Among the infants with ABO incompatibility all the mothers had O blood group, 31 mothers had A blood group and three mothers had B blood group. Seventeen of the 34 mothers who had ABO incompatible babies were primiparous (50 per cent) and 17 of them were multiparous (50 per cent). All mothers who had Rh incompatible infants were multiparous.

There was no significant difference between the groups with respect to age, gestational age, birthweight, hemoglobin, bilirubin and reticulocyte levels on admission (Table 3). There was no need for exchange transfusion in group I. In group II, exchange transfusion was performed in three out of 20 infants (12 per cent), and in the control group, seven infants required exchange transfusion. One infant from the control group also required two exchange transfusions. The rate of exchange transfusion in the multiple doses IVIG treatment group, group I, was lower than group II ($p < 0.05$) and the control group ($p < 0.01$). Also the rate of exchange transfusion in group II was lower than the control group ($p < 0.05$).

TABLE 2
Distribution of cases according to blood group incompatibility

	Group I (*n*)	Group II (*n*)	Group III (*n*)	Total
ABO incompatibility	11	11	12	34
Rh incompatibility	7	6	5	18
Subgroup incompatibility	1	–	1	2
More than one incompatibility	1	3	3	7
Total	20	20	21	61

TABLE 3
Characteristics of cases

	Group I	Group II	Group III
Patient number	20	20	21
Age (day)	2.3 ± 1.8	2.0 ± 1.6	2.8 ± 2.0
Gestational age (weeks)	39.2 ± 1.3	39.4 ± 1.4	39.1 ± 1.2
Birth weight (g)	3156 ± 380	3180 ± 420	3216 ± 464
Hemoglobin level (g/dl)	15.5 ± 2.6	15.6 ± 2.4	13.8 ± 2.1
Bilirubin level (mg/dl)	13.8 ± 5.4	13.5 ± 6.2	13.0 ± 5.7
Reticulocyte count (%)	3.4 ± 0.8	3.0 ± 1.1	2.9 ± 0.6
Duration of phototherapy (days)	2.8 ± 1.3	3.7 ± 2.1	4.5 ± 1.8
Number of exchange transfusions	–	3	7

Values shown as mean ± SD.

Duration of phototherapy was 2.8 ± 1.3 days in group I, 3.7 ± 2.1 days in group II, and 4.5 ± 1.8 days in group III. The differences were significant between groups I and III ($p < 0.01$), and also between groups II and III ($p < 0.05$). No significant differences were found between groups I and II. The hemoglobin levels were compared in all three groups on admission and 1 week after treatment. There were no differences within the groups (Table 4).

Discussion

IVIG has been used successfully in the treatment of several diseases caused by immune system disorders, such as autoimmune thrombocytopenic purpura, neonatal isoimmune thrombocytopenic purpura, Kawasaki disease, and Guillain-Barre syndrome.[13–18] In recent years, it has been shown that IVIG has been effective in the treatment of neonatal hemolytic jaundice due to ABO and Rh blood group incompatibility.[3,6,11] First studies were published in the early 1990s.[3,19] They were performed without control groups and the number of cases was low. Rubo published the first case-control study in 1992.[20] In this study the rate of exchange transfusion was 12.5 per cent in the IVIG treated group and 60 per cent in the control group. In a study that has been carried out in Turkey, the exchange transfusion rate in Rh blood group incompatible infants who were given IVIG, was found to be 20 per cent and in the control group 60 per cent.[6]

The rate of exchange transfusion in hemolytic jaundice is high in our country. Alp, *et al*. showed that 69.4 per cent of babies who were admitted to the hospital because of newborn hemolytic jaundice received exchange transfusion.[21] The exchange transfusion rate of our control group was lower than recorded by Alp, *et al*. This might be due to the relatively early hospitalization of our cases. Most of our cases were delivered in the obstetrics department of our hospital and were then closely monitored. The mean admission of our cases was 2.2 days, but in Alp's study it was 6.1 days.

Although IVIG is effective in the treatment of neonatal immune hemolytic jaundice, its effect is variable. With IVIG administration, the exchange transfusion rate varies in different studies.[6,20] The admission time of cases, duration and strength of phototherapy given, and dose and administration time of IVIG, may influence the response to treatment. Furthermore, the severity of hemolysis could affect the results; if isoantibody titer is high, it would exceed the effect of IVIG and hemolysis would continue.

Hammerman, *et al*. investigated the CO Hb (carboxy hemoglobin) level, which shows the degree of hemolysis, in infants who were given IVIG because of newborn hemolytic jaundice. They found that the CO Hb level was higher in cases who did not give an adequate response to IVIG administration.[9] In other words, when the hemolysis is higher, the response to IVIG will be lower. In our study, the cases that were given multiple doses of IVIG treatment did not require exchange transfusion. But in the single dose IVIG group, exchange transfusion rate was required in 12 per cent. It was thought that

TABLE 4
Hemoglobin values (g/dl) on admission and 1 week after the treatment

	Group I	Group II	Group III
Hb levels on admission	15.5 ± 2.6	15.6 ± 2.4	13.8 ± 2.1
Hb levels after 1 week treatment	14.0 ± 2.4	13.9 ± 2.7	12.9 ± 1.5

$p > 0.05$.

single dose IVIG reduced the need of exchange transfusion when compared to the control group. Multiple doses IVIG also blocked ongoing hemolysis despite the single dose treatment. These data indicate that the frequency of exchange transfusion could be significantly reduced by using multiple doses of IVIG.

Ergaz, *et al*. used the CO Hb test to investigate hemolysis reduction by IVIG. They showed that IVIG reduced the severity of jaundice in neonatal immune hemolytic disease by lowering the hemolysis.[11] One week later when we looked at the Hb levels of our patients, within all groups no significant differences were found (Table 4). But long-term follow-up of Hb levels will be necessary for evaluation of ongoing hemolysis and late anemia.

IVIG treatment decreased the duration of phototherapy causing the hospitalization duration to be shortened. Although multiple doses IVIG treatment cost is higher than exchange transfusion, shorter hospitalization time in IVIG treatment and severe complications in exchange transfusion (such as mortality) make IVIG treatment more favourable.

With IVIG treatment backache, headache, flushing, and wheezing could occur depending on the infusion rate. Also, although rarely, renal insufficiency, aseptic meningitis, allergic reactions, Coombs positive hemolytic anemia could be found.[22–24] No side-effects were seen in our cases. In conclusion, we think that the use of IVIG with phototherapy in the treatment of neonatal isoimmune jaundice due to blood group incompatibility will reduce the need of exchange transfusion and will shorten the duration of phototherapy. Furthermore, multiple doses of IVIG administration seems more able to prevent hemolysis.

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