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Antenatal treatment of fetal alloimmune cytopenias*

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Summary. The antenatal use of intravenous immunoglobulin (IVG) was explored in 9 cases of alloimmune cytopenias affecting fetuses. In 7 cases of alloimmune thrombocytopenia, IVG at a dose of 1 gm/kg/week appeared to be uniformly effective in elevating the fetal platelet count and preventing a recurrence of antenatal intracranial hemorrhage (2 cases). In 2 cases of Rh disease the results were more equivocal. There did not appear to be any significant toxicity associated with its use. The mechanism of IVG effect in the successfully treated cases remains uncertain.

Key words: Fetal – Alloimmune thrombocytopenia – Hemolytic anemia – Gammaglobulin

Introduction

Fetal and neonatal alloimmune cytopenias have antenatal consequences in severely affected cases. Both alloimmune hemolytic disease (Rh disease) and alloimmune thrombocytopenia may begin early in gestation and result in death of the fetus prior to birth. This manuscript considers the possible advances in therapy in these two similar diseases by describing the effects of giving intravenous immunoglobulin (IVG) to mothers prior to the birth of an affected fetus.

Neonatal alloimmune hemolytic disease (Rh disease) results in severe fetal anemia with development of hydrops fetalis in some cases. If untreated, there is a high mortality in these cases [2, 9]. Previous treatment entailed intraperitoneal transfusions of the fetus which themselves had a high morbidity and mortality. Currently management involves in utero intravascular transfusions, including exchange transfusions, but there is still a significant mortality. PUBS must be performed a minimum of 4–6 times per case and this can be very difficult in certain cases. In addition there are anecdotal fatalities even in cases that seem to be appropriately managed and receive at least one in utero red cell transfusion. Three anecdotal cases exist of successful use of IVG in patients with Rh disease [1, 6]. The rational for this use is to decrease the need for in utero transfusions and to lower mortality in severely affected cases by preventing the development of fetal hydrops until red cell transfusions may be started.

In neonatal alloimmune thrombocytopenia it has recently been recognized that as many as 25% of all intracranial hemorrhages occur antenatally [4, 7]. Despite these antenatal hemorrhages, the mortality is probably lower than in Rh disease, even in severely affected cases. However, mortality from the disease is often unrecognized and even in recognized affected cases, in utero transfusions cannot be successfully used because platelets would have to be given weekly instead of three-weekly which is not feasible. In addition, even if a treatment was available it is not clear whom to treat. Having a low platelet count is not incompatible with normal in utero development and certainly many fetuses who are severely thrombocytopenic in utero do not suffer an intracranial hemorrhage and have no sequelae of their thrombocytopenia [8]. Therefore the only clearcut indication for antenatal therapy is the subsequent fetus where the preceding infant has had an in utero intracranial hemorrhage.

This study investigated the usefulness of intrapartum IVG therapy in the two alloimmune cytopenias. In Rh disease the intent of IVG treatment was to supplement the in utero transfusion. In neonatal alloimmune thrombocytopenia, the intent was to

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use IVG as the sole therapy and see if it would elevate the fetal platelet count.

Materials and methods

The patients treated in this protocol (2 with Rh disease and 7 with NAIT) were selected because in all cases the preceding infant(s) had been severely affected. The two patients with immune hemolytic disease had specificities of anti Kell in patient no. 1 and Rh in patient no. 2. Both patients were sampled at 2 and then 3 week intervals and transfused in utero as needed (see case reports). 7 patients with NAIT (all anti-PI^{A1}) were infused with intravenous gammaglobulin (sandoglobulin, kindly provided by Sandoz US, East Hannover NJ) at a dose of 1 gm/kg/week. 5/7 patients with NAIT received dexamethasone in addition to IVG at doses of 5 mg/day in cases 1–3 and 3 mg/day in cases 4–5. PUBS was performed as previously described. The protocol of study was to perform a PUBS at 20–22 weeks or at referral and then to initiate treatment. PUBS was then repeated 4–6 weeks later to assess the effect of therapy. The protocol of study was approved by the Institutional Review Board of the New York Hospital and all patients gave permission for treatment. The results of treatment of the NAIT cases will be published elsewhere in greater detail [5].

Case reports

Neonatal immune hemolytic anemia

Case 1. The mother was a 33 year old 2 gravida 1 para (G2P1) with a high titer anti-Kell antibody secondary to a previous red cell transfusion. The first baby was born at 28 weeks gestation for anemia and required an exchange transfusion and additional red cell transfusions. This baby was sampled at 21 weeks gestation and had a hct of 32 with a 4+ direct Coombs; a red cell transfusion was given and IVG was initiated at weekly intervals. Repeat hcts at 3 week intervals remained between 30% and 35%; the fetus was never hydropic. One more red cell transfusion was given at 24 weeks gestation. The baby was electively delivered at 38 weeks gestation with a normal hct without incident.

Case 2. The mother was a 26 year old who had had a previous in utero demise secondary to Rh disease. She was referred at 27 weeks with a hydropic fetus. Hct at PUBS was 9% and an exchange transfusion was performed. IVG was begun 1 week later. Repeat hct 10 days later was 19% and another transfusion was given. 3 weeks later the hct was 26% and another transfusion was given. No effect of IVG could be discerned and in utero transfusions were continued until delivery.

Neonatal alloimmune thrombocytopenia

Case 1. A 40 year old gravida 4 para 1 abortus 2 (4G1P2A) mother had borne a baby with a platelet count of 3×10^9/l and an intracranial hemorrhage who died one day after birth. The hemorrhage was demonstrated by computerized tomography and confirmed at autopsy to have occurred antenatally at approximately 32 weeks of gestation. During her next pregnancy plasmaphoresis was attempted but she had an anaphylactoid reaction during her first course of this therapy at 23 weeks gestation. She subsequently received combined IVG and dexamethasone from 24 through 31 weeks of gestation. After amniocentesis and documented fetal lung maturity, the baby was delivered electively by caesarian section at 32 weeks gestation. The infant weighted 1400 grams at birth, had Apgar scores of 9 and 9 at 1 and 5 min respectively and had a platelet count of 30×10^9/l. After an exchange transfusion followed by transfusion of 1 unit of matched (not maternal) PL^{A1} platelets, the baby's platelet count remained greater than 100×10^9/l. Cranial ultrasonography was normal. The infant was discharged at 4 weeks of age at weight of 2200 grams and is now a normal 4 year old.

Case 2. The first child of a 25 year old gravid 3 para 2 white female was apparently unaffected; no neonatal platelet counts has been obtained. The second child was clinically well but had petechiae and purpura at birth. The initial platelet count of this child was 30×10^9/l; it subsequently fell to 14×10^9/l. Sonogram revealed no intracranial hemorrhage. At 20 weeks gestation during the current pregnancy, a fetal platelet count of 38×10^9/l was determined by PUBS. IVG and dexamethasone treatment were instituted and on repeat fetal blood sampling five weeks later the fetus' platelet count had increased to 195×10^9/l. PUBS repeated again at 32 and 37 weeks gestation revealed platelet counts of 112×10^9/l and 70×10^9/l respectively. Elective induction of labor was started, but because of failure to progress, delivery was accomplished by caesarian section. The baby was a 2865 gram healthy girl with Apgar scores of 9 and 9. The platelet count at birth was 64×10^9/l but then fell to 28×10^9/l 6 hours later. Washed maternal platelets were infused and the platelet count remained persistently 100×10^9/l. Cranial ultrasonography was normal. The infant had an uneventful neonated course and was discharged with the mother on the sixth day of life.

Case 3. The mother was a 26 year old gravida 2 para 1. The first baby was delivered by caesarean section for failure to progress and had a platelet count of 15×10^9/l. Intracranial hemorrhage, as determined by ultrasonography, did not occur. With the second pregnancy the fetal platelet count at 27 weeks was found by PUBS to be 13×10^9/l. Treatment was initiated with IVG and dexamethasone and at 32 weeks the platelet count was 26×10^9/l. Delivery was accomplished by elective caesarean section at 35 weeks. The baby weighed 2450 gram and had Apgar scores of 8 and 9 at 1 and 5 min respectively. The cord blood platelet count was 50×10^9/l, falling to 42×10^9/l 12 h after birth. 400 mg/kg of IVG was infused followed by washed maternal platelets. All subsequent platelet counts were greater than 100×10^9/l. No evidence of an intracranial hemorrhage was detected by ultrasonography. The infant had an uneventful neonatal course and was discharged on the twenty-second day of life.

Case 4. The mother was a 30 year old gravida 2 para 1 woman whose first child had had a platelet count of 10×10^9/l at birth. During the current pregnancy a fetal platelet count of 92×10^9/l at 31 weeks gestation was measured by PUBS. IVG and dexamethasone were begun. The fetal platelet count was 237×10^9/l at 37 weeks. Spontaneous rupture of membranes took place at 37 ½ weeks and vaginal delivery resulted in the birth of a 2750 gram baby with Apgar scores of 8 and 9. The platelet count was 235×10^9/l at birth and remained $> 200 \times 10^9$/l without therapy. No evidence of an intracranial hemorrhage was detected by CT and the neonate was discharged on the fourth day of life.

Case 5. A 32 year old gravida 2 para 1 woman had a baby 9 years previously with a platelet count at birth at 2×10^9/l. That infant had suffered an intracranial hemorrhage which may have occurred antenatally. The current fetus was conceived while the mother was on Pergonal and ultrasonography revealed the presence of sextuplets. Selective reduction procedures performed at 11 and 12 weeks resulted in a twin gestation. Because of the location of the cord insertion sites, PUBS could only by performed on one of the two viable fetuses. The platelet count of this fetus was 14×10^9/l at 22 weeks gestation. IVG and dexamethasone therapy was begun. Two weeks later both fetal heart sounds were normal but at 26 weeks gestation the unsampled twin was found to be dead in utero. The dead fetus was gradually resorbed. Further sampling was not attempted. After documenting fetal lung maturity, delivery was accomplished by elective caesarean section at 34 weeks gestation because of uncer-

tainty regarding the fetal platelet count and ultrasonic evidence of developing intrauterine growth retardation. The baby weighed 1450 grams and had Apgar scores of 3 and 9. The platelet count was 45×10^9/l at birth and this increased spontaneously to $> 100 \times 10^9$/l within 5 days without any therapy. No evidence of an intracranial hemorrhage was detected by ultrasonography. The infant had an uneventful neonatal course and was discharged on the twenty-third day of life.

Case 6. The mother was 28 year old gravida 2 para 1 woman, whose first child had a platelet count of 10×10^9/l at birth. Ultrasound did not demonstrate an intracranial hemorrhage. During the current pregnancy her fetus was found to have a platelet count of 130×10^9/l at 22 weeks gestation. Therapy was not initiated. PUBS was repeated at 28 weeks gestation and the fetal platelet count was determined to be 28×10^9/l. IVG alone was begun. The fetal platelet count was 79×10^9/l at 32 weeks gestations. PUBS was repeated at 37 weeks to determine the need for Caesarian section and the platelet count was found to be 139×10^9/l. The membranes was ruptured and a vaginal delivery was performed uneventually neonatal course and was discharged on the fourth day of life.

Case 7. The mother was a 30 year old gravida 4 para 1 female. The first pregnancy resulted in a miscarriage at 18 weeks gestation and the second pregnancy in an unexplained in utero demise at 23 weeks; no autopsy was performed. The third pregnancy resulted in a normal spontaneous vaginal delivery. Physical examination was normal except for the presence of petechiae; the platelet count was 15×10^9/l. Computerized tomography revealed a temporal lobe attributed to an intracranial hemorrhage estimated to have taken place approximately 6 weeks earlier. With the current pregnancy, PUBS at 20 weeks gestation revealed a platelet count of 13×10^9/l. The mother received IVG. PUBS at 25 weeks revealed a platelet count of 51×10^9/l. She is currently 30 weeks gestation.

Discussion

IVG appeared to be an effective treatment for neonatal alloimmune thrombocytopenia. Two patients (no. 1 and no. 7) did not have an intracranial hemorrhage despite the fact that their preceding siblings had suffered antenatal intracranial hemorrhages. The fetal platelet counts increased in 6/6 cases an average of more than 70×10^9/l (median $> 40 \times 10^9$/l). All platelet counts were $> 25 \times 10^9$/l after the initiation of treatment. There was no apparent effect of dexamethasone on the platelet increase and it appeared to be linked to the development of oligohydramnios. Comparing the treated infants to their preceding untreated siblings, the platelet counts in the treated infants were greater than in the untreated infants in every case despite the tendency of NAIT to worsen with time. The average increase in the platelet count for the subsequent treated siblings as compared to the previous untreated siblings was $> 70 \times 10^9$/l. In summary IVG administered to the mother was consistently effective in elevating the fetal platelet count and apparently prevented intracranial hemorrhage in 3 cases where the previous sibling had been affected (nos. 1, 5, and 7). The effects of IVG could be appreciated in NAIT either by comparing the treated fetus to the previous fetus or by comparing the serial platelet counts obtained by PUBS in each fetus.

The results of IVG treatment in the 2 cases of immune hemolytic anemia were not as good. IVG appeared to be effective in case 1 of Kell incompatibility but to have no effect in case 2. Even in case 1, the evidence of effect was entirely dependent upon the preceding sibling since the fetal hematocrit was never less than 30% (normal) in the treated fetus, although the fetus was $Kell^+$ and the direct Coombs 4^+ on the first PUBS. Three cases of apparent effectiveness of IVG in Rh disease have been reported but none have had severely affected previous fetuses and none were followed by serial PUBS. It is possible although unlikely that the discrepancy in IVG effect between the 2 cases was due to the different anti red cell antibody specificities. The apparent lesser effectiveness of IVG in antenatal treatment of hemolytic disease as compared to NAIT may be similar to the difference in treatment effect between autoimmune hemolytic anemia and ITP [3].

In summary, IVG appears to be an effective antenatal treatment of NAIT. All 7 fetuses seemed to have benefited from IVG as assessed both by serial fetal platelet counts determined by PUBS as well as by comparing the treated to the untreated previous affected fetus. The efficacy of IVG in alloimmune hemolytic disease was apparently less but more cases of both need to be treated to better understand the use and usefulness of IVG in these two diseases.

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