Late hyporegenerative anemia of Rhesus hemolytic disease

Fahri OVALI[1], Nedim SAMANCI[1], Türkan DAĞOĞLU[1], Oya ÇETİNKAYA[1], Ergin BENGİSU[2]

Depts. of [1]Obstetric&Gynaecology, [2]Neonatal Intensive Care Unit, Medical School of istanbul University, istanbul, TURKEY

The current therapy for fetuses affected by Rhesus (Rh) hemolytic diasease is intrauterine transfusions to prevent hydrops fetalis. After birth, these babies usually develop anemia in the second week of life, which requires erythrocyte transfuisons. The cause of this anemia may be ongoing hemolysis due to the Rh ahtibodies as well as low serum ertyhropoietin levels. Thirty-eight fetuses with Rh hemolytic disease with a mean gestational age of 35.1 ±2,3 weeks were delivered at our clinic. They had received a median of 3 intrauterine transfusions. Mean serum erythropoietin level at the time of deivery was 13.9+6.8 mU/ml. After the second week of life, these babies received median of 3 erythrocyte transfusions and their anemia was corrected at the end of the 11th week of life. The babies with Rh hemolytic disease should be followed up at least for 3 nonths and receive erythrocyte transfusions when necessary. The finding of low serum erythropoietin levels suggest that recombinant human erythropoietin therapy might be an alternative to such transfusions. [Turk J Med Res 1994; 12(6): 253-256]

Key Words: Anemia, Rh disease

The frequency of severe Rh hemolytic disease has declined considerably over the past decades, after the introduction of anti-D prophylaxis. However, new cases still occur, mainly due to failure to administer anti-D. In fetuses affected with Rh hemolytic disease, ultrasound guided intrauterine intravascular transfusions can treat anemia and reverse hydrops (1,2). Hyporegenerative anemia of these affected newborns is seen on the second to sixth week of life and it is associated with low reticulocyte counts and low serum erythropoetin levels (3,4). Conventional treatment for this kind of anemia is simple erythrocyte transfusions. However, recombinant human erythropoietin (rHEPO) treatment has assumed importance recently (3,5) and the results are promising.

Fetal intravascular transfusions for prevention of Rh hemolytic disease have been performed at our instution for the last 4 years. We report the outcomes of these patients, including the treatments for the late anemia.

Received: Oct. 7,1994 **Accepted:** Oct. 23, 1994

Correspondence: Fahri OVALI
Gulbayir Sok. 9/6
34010 Merter-istanbul-TURKEY

MATERIALS AND METHODS

The mothers were treated at Medical School of Istanbul University, Department of Obstetrics and Gynecology, Perinatology section and the babies were managed at the Neonatal Intensive Care Unit (NICU) within the same department. During the period between April 1992 and February 1994, all fetuses with Rh isoimmunization were considered eligible for the study. The disease was confirmed by maternal sensitization to the D antigen, the pr sence of fetal Rh factor and direct Coombs positivity of fetal blood.

Intrauterine transfusions were performed when fetal hemoglobin (Hb) values were <9 g/dl or hematocrit (Hct)<0.30. The number and timing of intrauterine transfusions (IUT) depended on the severity of the illness, the gestational age at which IUTs were begun and the rate of the fall of the fetal hematocrit.

The fetuses were delivered usually before term, by elective cesarean section and transferred to the Neonatal Intensive Care Unit (NICU). Initial Hct, Hb and reticulocyte values were determined at the time of delivery and daily thereafter and as often as clinically indicated. Serum erythropoetin (EPO) levels were determined at the time of delivery by enzyme linked immunosorbent assay (EPO-ELISA Medac GmbH, Hamburg). After discharge from the hospital, the babies were followed up by the same pediatricians

who were responsible for them at the NICU. Serial Hct, Hb and reticulocyte counts were determined weekly after discharge.

The previously mentioned criteria were used for erythrocyte transfusions at the follow up. When the Hct and Hb values remained stable for 3 weeks and reticulocyte counts began to increase, the anemia was said to be corrected and the babies were called only for monthly follow up examinations. Serum EPO levels were determined at the second week of life and after the stabilization of Hb values.

The period from birth to the time of the last transfusion was evaluated as the stabilization period.

Paired t test was used for statistical significance and a p value of <0.05 was considered significant. Values are described as mean+standard deviation (SD).

RESULTS

There were 38 fetuses eligible for the analyses. Demographic data pertaining to these fetuses are shown In Table 1. All but 5 patients received IUT. The mean number of IUT was 2.8±1.6 (range: 0-6) (Table 2). Mean gestational age for these babies was 35.1±2.3 weeks (range: 31-37 weeks) and mean birthweight was 2629±452 g (range: 1700-3700 g). Most of the babies were delivered before term by elective cesarean section. Mean Hb level at the time of delivery was 12.9±3.1 g/dl (range: 7.9-17.1) and concurrent mean Hematocrit level was 0.41 ±0.08 (range: 0.28-0.62). A total of 19 exchange transfusions were performed; hence the mean 0.5+0.6. Twentyone (58%) infants did not require any exchange transfusions whereas 3 infants required exchange transfusions twice (Table 3). The infants received phototherapy whenever their bilirubin values exceeded the appropriate curves of Oski and Naiman (6).

Five infants had exchange transfussions after the second postnatal week (Table 4). The mean number of transfusions was 3.0±1.0 (range: 1-5, median: 3). The 4 babies who had not required IUT also required 3 transfusions each. The mean stabilization period of Hb values, which was calculated as the period from birth to the time of the last transfusion was 10.9±2.5 weeks (range: 6-15 weeks, median: 11 weeks).

Serum b'PO levels were available for 31 patients. Mean EPO level at the time of delivery was 13.9±6.8 mU/ml (range: 4-31 mU/ml). EPO levels at the second week of life was 5.4±2.2 mU/ml (range: 2-10 mU/ml) and 33.6±14.5 mU/ml (range: 22-64 mU/ml) after the stabilization of Hb values (p<0.05).

The average reticulocyte count in the first day of life was 0.33% (range: 0.0-1.7%), 0.18% (range: 0.0-1.1) at the second week and increased to 2.9% (range: 1.4-5.3%) at the end of the stabilization period (p<0.05).

Table 1. Characteristics of the patients

Total number of fetuses	38
Male/female	20/18
Gestational age (median)	35 weeks
Birthweight (median)	2620 g
No. of IUT (median)	3

Table **2.** Intrauterine Transfusions (IUT)

No. of IUT	n	%
0	5	13
1	2	5
2	7	19
3	11	29
4	9	24
5	1	2
6	**3**	8
Total	38	100

Table 3. Exchange transfusions

No. of exch. transfusions	n	%
0	22	58
İ	13	34
2	3	8
Total	38	100

Table **4.** Erythrocyte transfusions

No. of transfusions	n	%
0	0	0
1	3	8
2	6	16
3	17	45
4	9	23
5	3	8
Total	38	100

All babies survived and they had attained their normal physical and neurological growth at 6 months postnatally.

DISCUSSION

Late anemia in infants with Rh hemolytic disease was described almost 40 years ago (2), occuring during the second to fifth weeks of life. Factors contributing to this anemia includes the reduced survival of the transfused cells and the reduced survival of the neonate's Rh positive cells caused by residual anti-D antibody and rapid body growth (8,9). The incidence of late anemia appears to be higher in infants who receive intravascu'ar intrauterine transfusions (4). On the other hand, Koening et al have found that serum EPO con-

centrations are low in these infants compared to infants without Rh hemolytic disease and this may contribute to the development of anemia also (3).

Thirty four of our 38 patients had received intrauterine transfusions for the prevention of hydrops fetalis. All of them developed late anemia, after the second week of life, as described In the literature (3,5,10). Interestingly, 4 patients who had not received IUT also developed late anemia and they received 3 transfusions each almost at the same time with the patients who received IUTs. However, since their number is so small, it is impossible to compare infants who received IUT with ones who did not with respect to the rate of late anemia.

The finding of low serum EPO levels is also consistent with the anemia of prematurity. The median gestational age of our patients was 35 weeks and there were even babies as young as 31 weeks. Therefore, anemia of prematurity may have contributed to the late anemia of Rh disease also. However, for technical reasons, it was difficult to determine to which degree prematurity contributed to the late anemia of Rh disease. Nevertheless, low serum EPO levels and reticulocyte counts are also found in the anemia of prematurity.

The infants had received a median of 3 IUT each and it was possible to prevent hydrops fetalis in all babies. 58% of these babies did not require exchange transfusions. However, 45% of babies required erythrocyte transfusions for late anemia 3 times (Table 4) during a median of 11 weeks. The values are all comparable to literature (4,5). Serum EPO levels rose concurrently during this period. Koenig et al and Ohls et al have proposed that EPO therapy might be an alternative to erythrocyte transfusions (4,5).

The low reticulocyte count in the first day of life was parallel to the low EPO levels. At the end of the stabilization period, the reticulocyte count increased with the increase of EPO levels and approximated to the normal reticulocyte counts at the 10th week of life.

Although no comparative data exists regarding the normal serum EPO levels at 35 weeks of gestation, when compared with those of term infants, EPO levels were lower than expected at the time of delivery and inappropriately low to the degree of anemia thereafter. The possible reason might be that fetal erythroid precursors are exquisitely sensitive to minimal amounts of EPO (11). EPO is produced by the liver in utero and it is less responsive to hypoxic stimulus than EPO produced by the kidney in later gestation and life. IUT might also delay normal maturational shift of EPO production from liver to kidney (4). It is possible that anti-D IgG might inhibit EPO production or at least blunt EPO activity. These factors lead the way to the use of rHEPO for the treatment of late anemia of Rh hemolytic disease as it has been at the anemia of prematurity. A prospective, double blind placebo controlled study is under way at our institution for this purpose.

Since Rh hemolytic disease is a continuing medical problem, we should be aware of its late consequences such as anemia and take necessary measures to prevent and to treat it. Definitely, the best preventive measure would be to prevent the native disease, that is Rh hemolytic disease.

Rh hemolitik hastalıkla geç anemi

Rhesus (Rh) hemolitik hastalıklı fetusların halihazır tedavisi, hidropsu önlemek için yapılan intrauterin intravasküler transfüzyonlardır. Doğumdan sonra bu bebeklerde, genellikle 2.haftada eritrosit transfüzyonunu gerektirecek bir anemi ortaya çıkar. Bu aneminin nedeni, Rh antikorlarına bağlı olarak devam eden hemoliz olabileceği gibi, düşük serum eritropoetin düzeyleri de olabilir. Kliniğimizde doğan ve ortalama gestasyonel yaşları 35.1±2.3 hafta olan Rh hemolitik hastalıklı 38 bebek incelemeye alındı. Bu bebeklere ortalama 3 kez intrauterin transfüzyon yapılmıştı. Doğumdaki ortalama serum eritropoetin düzeyleri 13.9±6.8 mU/ml idi. İkinci haftadan sonra bu bebekler ortalama 3 kez eritrosit transfüzyonu aldılar ve doğumdan sonraki 11.haftada bu bebeklerin anemileri düzeldi. Rh hemolitik hastalıklı bebekler doğumdan sonra en az 3 ay izlenmeli ve gerektiğinden eritrosit transfüzyonları yapılmalıdır. Düşük serum eritropoetin düzeylerinin bulunması, rekombinan human eritropoetin tedavisinin bu transfüzyonlara bir alternatif olabileceğini düşündürmektedir. [Türk J Med Res 1994; 12(6): 253-256]

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