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Neonatal management and outcome in red cell alloimmunization

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Exchange transfusions and top-up transfusions in neonates with Kell hemolytic disease compared to Rh D hemolytic disease

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Abstract

Objective: To evaluate neonatal outcome in Kell hemolytic disease compared to Rh D hemolytic disease.

Study design: Retrospective study of all (near)-term neonates with Kell (n=34) and Rh D hemolytic disease (n=157) admitted to our center between January 2000 and December 2008. We recorded the need for exchange transfusion and top-up transfusions up to three months of age.

Results: Neonates in the Kell group required less days of phototherapy than neonates in the Rh D group (2.4 versus 4.1 days, respectively ($p < 0.01$)). The percentage of neonates requiring an exchange transfusion was lower in the Kell group than in the Rh D group (6% (2/34) and 62% (98/157), respectively ($p < 0.01$)). The percentage of neonates in the Kell group and Rh D group requiring a top-up transfusion was 62% (21/34) and 72% (113/157), respectively ($p = 0.20$). The median number of top-up transfusions per neonate in the Kell group and Rh D group was 1 (interquartile range (IQR) 0-2) and 2 (IQR 0-2), respectively ($p = 0.07$).

Conclusion: Neonates with Kell hemolytic disease require less phototherapy and less exchange transfusions compared to neonates with Rh D hemolytic disease, but an equal number of top-up transfusions.

Introduction

Kell alloimmunization is second only to Rh D in causing antibody-mediated fetal anemia. Since the introduction of Rh D immunoprophylaxis, Kell antibodies account for 10% of antibody-mediated fetal anemia.¹ After introduction of routine antibody-screening of all pregnant women in the Netherlands in 1998, perinatal survival of fetuses with Kell hemolytic disease of the neonate (HDN) treated with intrauterine transfusion (IUT) increased from 61% to 100%.²

In contrast to Rh D HDN, fetal anemia in Kell HDN is often more severe due to concomitant suppression of erythropoiesis rather than hemolysis of erythrocytes.³⁻⁵ Consequently, the immediate neonatal management in Kell HDN is different from Rh D HDN. A previous small study showed that neonates with Kell HDN have lower serum bilirubin levels and require less phototherapy and exchange transfusions (ETs) than neonates with Rh D hemolytic disease.⁶

In analogy with Rh D hemolytic disease, neonates with Kell HDN may require top-up transfusions for up to several months after birth.⁷ Whether the incidence and severity of neonatal anemia in Kell hemolytic disease differs from neonates with Rh D hemolytic disease, is not known. Only a limited number of studies (mostly case reports) have been published on the severity of anemia in the postnatal period.^{6, 8-10}

The aim of this study was to evaluate neonatal and hematological outcome in a large series of neonates with Kell hemolytic disease compared to neonates with Rh D hemolytic disease.

Materials and Methods

All (near)-term neonates (gestational age ≥ 35 weeks) with hemolytic disease due to maternal Kell and Rh D alloimmunization, delivered between January 2000 and December 2008 at the Leiden University Medical Center (LUMC) were included in this retrospective observational study. Part of the neonates included in the Rh D group have previously been described in a different study.¹¹ Our center is the national referral center for the management and intrauterine treatment of red cell alloimmunization in the Netherlands. We excluded all neonates with other types of HDN and neonates participating in an ongoing randomized trial for the use of immunoglobulin in Rh D hemolytic disease, which started in August 2006 at our institution (LIVIN study: <http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=832>).

The guideline for the application of phototherapy at our neonatal division has previously been described.^{11,12} The guidelines for ET used at our neonatal division were changed in December 2005. Before December 2005, criteria for ET included: (1) bilirubin level at birth > 3.5 mg/dL (so-called early criterion) and/or (2) total serum bilirubin level above ET thresholds (rise of bilirubin value > 0.5 mg/dL/hr despite intensive phototherapy). In neonates not treated with IUT, a hemoglobin level at birth of < 12.9 g/dL was also considered as an early criterion for ET.¹² In December 2005 a new guideline of the American Academy of Pediatrics (AAP) with higher bilirubin thresholds for phototherapy and ET was implemented by our department.¹³ The criteria for ET after December 2005 were: (1) total serum bilirubin above (higher) ET thresholds¹³ and/or (2) rise of bilirubin > 0.5 mg/dL/hr despite intensive phototherapy, and/or (3) clinical symptoms of acute bilirubin encephalopathy regardless of bilirubin level. ET was performed with double-volume transfusion (160 mL/kg) using irradiated and leukocyte-depleted compatible erythrocytes.

We recorded the following obstetric and neonatal data: fetal hemoglobin concentration at first IUT and number of IUTs, gestational age at birth, birth weight, hemoglobin level and reticulocyte count at birth, bilirubin level at birth, maximum bilirubin level during admission, duration of phototherapy (days), number of ETs required, number of top-up red blood cell transfusions received during the first 3 months of life and hemoglobin levels prior to the top-up transfusion. Data on the number of top-up transfusions and hemoglobin levels prior to the top-up transfusion in infants who received follow-up outside the LUMC were collected through correspondence with the local pediatrician or blood transfusion department. After discharge from our center, top-up transfusions were performed in referring hospitals when hemoglobin levels were < 8.0 g/dL, or < 9.6 g/dL if clinical symptoms of neonatal anemia were present (such as lethargy, feeding problems, need for oxygen or failure to thrive). Folic acid (50 mcg/day) was administered orally during the first three months of life to all neonates with hemolytic disease.

Primary outcome was the number of ETs and the number of top-up transfusions. Outcome was compared between neonates with Kell hemolytic disease (Kell group) and neonates with Rh D hemolytic disease (Rh D group).

Data are reported as means and standard deviations (SD) or as medians and interquartile range (IQR), as appropriate. Statistical analysis was performed using Student-t-test and Mann-Whitney test for continuous variables. Chi square and Fisher's exact test were used for categorical variables, as appropriate. Linear regression analysis was performed using the Pearson Correlation coefficient. A p-value < 0.05 was considered statistically significant. Statistical analysis was executed with SPSS 16.0 (SPSS Inc, Chicago, IL, USA).

Results

During the study period, 309 neonates with hemolytic disease were admitted to our neonatal nursery. Two hundred and seventy-seven (90%) of these neonates were delivered at a gestational age ≥ 35 weeks. Fifty-five neonates were excluded because of participation in a randomized trial for the use of intravenous immunoglobulin. Thirty-one neonates were excluded due to HDN caused by Rh c (n=17), Rh C (n=3), Rh E (n=3), Cw (n=2), Jka (n=1), presence of both Rh D and Kell antibodies (n=2), and unknown type of irregular antibody (n=3). A total of 191 patients were included in this study, 34 (18%) in the Kell group and 157 (82%) in the Rh D group. Baseline characteristics in both groups are summarized in Table 1. Intrauterine transfusions (IUTs) were performed in 82% of neonates in the Kell group and 66% of neonates in the Rh D group ($p = 0.07$). The median number of IUTs in the Kell group and Rh D group was 3 (IQR 2-4, range 0-5) and 2 (IQR 0-4, range 0-6) respectively ($p = 0.01$). In the Kell group the median antibody titer at first IUT was 1:128 (range 1:2-8000).

Table 1 Baseline characteristics in neonates with Kell and Rh D hemolytic disease

	Kell (n = 34)	Rh D (n = 157)	p-value
Neonates treated with IUT – n (%)	28 (82)	104 (66)	0.07
Number of IUTs per neonate ^a	3 (2-4)	2 (0-3.5)	0.01
Gestational age at first IUT – weeks ^a	27 (23-29)	29 (24-33)	0.07
Hemoglobin level at first IUT – g/dL ^a	5.3 (3.5-7.3)	6.4 (5.0-7.4)	0.16
Gestational age at birth – weeks ^a	36 (36-37)	37 (36-37)	0.52
Birth weight – grams ^b	3190 $\pm$ 348	2947 $\pm$ 418	<0.01
Male – n (%)	25 (74)	92 (59)	0.11

^a Value given as median (IQR)

^b Value given as mean $\pm$ SD

Phototherapy and ET

Detailed information on neonatal outcome in both groups, in particular treatment with phototherapy and ET is presented in Table 2. Mean bilirubin level at birth and maximum bilirubin level during admission were significantly lower in the Kell group than in the Rh D group, 3.1 versus 6.0 mg/dL ($p < 0.01$) and 8.0 versus 14.3 mg/dL ($p < 0.01$), respectively. Neonates in the Kell group required significantly less days of phototherapy than neonates in the Rh D group (2.4 and 4.1 mean days, respectively, ($p < 0.01$)). At least one ET was required in 6% (2/34) of the patients in the Kell group compared to 62% (98/157) of the patients in

the Rh D group ($p < 0.01$). The median number of ETs was 0 in the Kell group (IQR 0-0, range 0-1) and 1 in the Rh D group (IQR 0-1, range 0-5) ($p < 0.01$). None of the infants in the Kell group without IUT required an ET.

Top-up transfusions

Complete information on the number of top-up red cell transfusions was obtained for 98% (188/191) of neonates. The percentage of neonates requiring a top-up transfusion was similar in the Kell group and Rh D group (62% (21/34) and 72% (113/157), respectively ($p = 0.20$). The median number of top-up transfusions per neonate in the Kell group and Rh D group was 1 (IQR 0-2, range 0-4) and 2 (IQR 0-2, range 0-6), respectively ($p = 0.07$). Mean hemoglobin level at first top-up transfusion and median number of days until first top up transfusion were similar in both groups. Detailed information on the use of top-up transfusions in the Kell group and Rh D group is presented in Table 3.

In the sub-group analysis of neonates treated with IUT ($n=132$), we found that neonates with Rh D HDN required significantly more top-up transfusions than neonates with Kell HDN (median of 2 range 0-6 and median of 1 range 0-4), respectively ($p = 0.02$). We performed a linear regression analysis between the number of IUTs and the reticulocyte count at birth in both groups. A higher number of IUTs was correlated with a lower reticulocyte count at birth in the Rh D group (Pearson Correlation coefficient -0.49; $p < 0.001$). This negative correlation was not found in the Kell group (Pearson Correlation coefficient -0.05; $p = 0.85$).

Table 2 Neonatal outcome in the Kell and Rh D group

	Kell (n = 34)	Rh D (n = 157)	p-value
Hemoglobin level at birth - g/dL ^a	7.9 ± 1.8	7.2 ± 1.6	0.01
Bilirubin level at birth - mg/dL ^a	3.1 ± 1.7	6.0 ± 2.3	<0.01
Reticulocyte count at birth – % ₀₀ ^{b,c}	12 (8-49)	21 (3-66)	0.90
Maximum bilirubin – mg/dL ^b	8.0 (3.9-10.7)	14.3 (10.8-16.9)	<0.01
Neonates treated with phototherapy – n (%)	31 (91)	154 (98)	0.07
Phototherapy – days ^{a,d}	2.4 ± 1.3	4.1 ± 1.7	<0.01
Neonates treated with ET – n (%)	2 (6)	98 (62)	<0.01
Number of ETs per neonate ^b	0 (0-0)	1 (0-1)	<0.01

^a Value given as mean ± SD

^b Value given as median (IQR)

^c Reticulocyte count at birth was assessed in 15/34 and 81/157 neonates in the Kell and Rh D-group, respectively

^d Days of phototherapy was assessed in 134/157 neonates with Rh D

Table 3 Top-up transfusions in neonates with Kell and Rh D hemolytic disease

	Kell (n = 34)	Rh D (n = 157)	p-value
Neonates requiring top-up transfusions – n (%)	21 (62)	113 (72)	0.20
Number of top-up transfusions per neonate ^a	1 (0-2)	2 (0-2)	0.07
Neonates requiring:			
1 top-up transfusion – n (%)	10 (48)	39 (35)	0.62
2 top-up transfusions – n (%)	8 (38)	40 (35)	0.77
3 top-up transfusions – n (%)	2 (9)	16 (14)	0.54
4 top-up transfusions – n (%)	1 (5)	14 (12)	0.31
5 top-up transfusions – n (%)	0 (0)	2 (2)	1.00
6 top-up transfusions – n (%)	0 (0)	1 (1)	1.00
Days after birth until first top-up transfusion ^a	16 (1-31.5)	17.5 (1-33.5)	0.56
Hemoglobin level at first top-up transfusion – g/dL ^b	8.2 ± 1.4	8.4 ± 1.5	0.73
Number of top-up transfusions (per neonate) in the subgroup treated with IUT ^a	1 (0-2)	1.9 (1-3)	0.02

^a Value given as median (IQR)^b Value given as mean ± SD

Comment

This study shows that fetuses with severe Kell hemolytic disease are more often treated with IUT compared to fetuses with Rh D hemolytic disease. Subsequently, infants with HDN due to Kell-antibodies need less phototherapy and ETs in the neonatal period than neonates with Rh D hemolytic disease. However, the need for top-up transfusions was similar in both groups.

Various researchers have suggested that anemia in Kell hemolytic disease is caused primarily by erythroid suppression rather than hemolysis, as in Rh disease.^{3,4} An alternative theory is that anti-Kell-antibodies are responsible for the destruction of early erythroid progenitor cells, which lack hemoglobin.^{5,14} A lower amniotic fluid bilirubin and only mild neonatal hyperbilirubinemia in Kell hemolytic disease compared to Rh D are consistent with this theory. In addition, an in vitro study by Vaughan et al. demonstrated that human monoclonal anti-Kell antibodies and the serum of women with anti-Kell antibodies specifically inhibit the growth of Kell-positive erythroid progenitor cells.⁵ Vaughan et al. found no correlation between the anti-Kell antibody titer and the degree of inhibition.⁵ Poor correlation between antibody titer and disease severity in Kell supports the theory that Kell alloimmunization

has a different pathogenesis than Rh alloimmunization. In a recent study of 43 pregnancies with Kell alloimmunization, we found that the vast majority of severely affected cases had antibody titers of 1:32 or more. Nevertheless, to be on the safe side, we recommended that all pregnancies with Kell titers of 1:2 or higher (and a proven Kell positive fetus) should be closely monitored.²

In accordance with previous studies from the group of Weiner⁴ and our group¹⁵ we found that antenatal course of fetuses with Kell alloimmunization is different from Rh D hemolytic disease. Fetuses with Kell alloimmunization have lower hemoglobin levels at first IUT and require more IUTs. Moreover, the first IUT was performed at an earlier gestational age than in Rh D fetuses.¹⁵ These findings underscore that fetal anemia is more severe in Kell sensitized fetuses than in Rh D sensitized fetuses. Weiner et al. also found a significant lower reticulocyte count, reflecting the destruction of Kell expressing erythroid progenitor cells in Kell hemolytic disease.⁴

In terms of neonatal management and outcome, this study shows that neonates with Kell hemolytic disease have milder hyperbilirubinemia, requiring less phototherapy and ETs than infants with Rh D hemolytic disease. In our study we found no relation between lack of IUT and number of ETs or top-up transfusions. Our findings are consistent with previous reports^{6,8,16-18} and reflect the observation that hemolysis of mature (hemoglobinised) erythrocytes in Kell hemolytic disease is less than in Rh D hemolytic disease.^{3,4}

Given the significantly higher number of IUTs in the Kell group, one could expect an increased incidence of postnatal anemia (and top-up transfusions). As shown in previous studies, repeated IUTs result in a decreased reticulocyte count, indicating a suppression of fetal erythropoiesis.^{12,19} In contrast, we found a trend towards less top-up transfusions in neonates with Kell hemolytic disease compared to neonates with Rh D hemolytic disease, however this difference was not significant ($p = 0.07$). This finding could support the fact that fetal and neonatal anemia due to Kell alloimmunization has a different pathogenesis than Rh alloimmunization. Larger studies are required to confirm these findings. In contrast to anti-D, most anti-Kell antibodies have a strong lytic potential which also affects red cell precursor cells.^{3,4,19} Vaughan and colleagues found no correlation between the antibody titer and the degree of inhibition of Kell-positive erythroid progenitor cells. The titers of anti-Kell antibodies associated with fetal anemia are generally substantially lower compared to ten to 100 fold higher titers in case of Rh D hemolytic disease. Consequently anti-D antibodies may circulate in the newborn for a longer period after birth, whereas Kell antibodies disappear sooner, which may explain the more moderate late anemia in Kell hemolytic disease, despite concomitant suppression of the erythropoiesis.⁵

This is the first study comparing the degree of postnatal anemia in a relatively large number of infants with Kell- and Rh D hemolytic disease. Santiago et al. described three neonates with Kell HDN of whom only one required a top-up transfusion.¹⁷

Collinet et al. reported a case of severe fetal anemia due to Kell alloimmunization, which was postnatally treated with two top-up transfusions and recombinant erythropoietin and iron supplementation.⁷

The results of this study should be interpreted with care due to the small number of neonates with Kell hemolytic disease in this study which is inherent to the low incidence of this disease. Larger, multicenter studies are required to confirm our findings.

In conclusion, although neonates with Kell hemolytic disease require less phototherapy and exchange transfusions, the equal need for top-up transfusions justifies similar follow-up management as in Rh D hemolytic disease. Finally, because of the destruction of red cell precursor cells as well, treatment with erythropoietin may be more effective in neonates with Kell hemolytic disease than in neonates with Rh D hemolytic disease.^{9,10}

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