Neonatal management and outcome in red cell alloimmunization

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Neonatal morbidity after exchange transfusion for red cell alloimmune hemolytic disease

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Abstract

Objective: Our aim was to study the type and rate of complications associated with exchange transfusion (ET) in a large series of neonates with hemolytic disease of the newborn (HDN) due to red cell alloimmunization.

Patients and Methods: All neonates with HDN due to red cell alloimmunization admitted to our center between January 2001 and June 2011 were eligible for this study. We recorded the number and rate of complications during admission in the group of neonates treated with (ET-group) and without ET (no-ET-group). Multivariate logistic regression analysis was performed to measure independent risk of complications of ET treatment.

Results: A total of 347 infants with red cell alloimmune hemolytic disease were included, 39% (134/347) was treated with at least one ET during admission (ET-group) and 61% (213/347) did not require ET (no-ET-group). Comparison between the ET-group and no-ET-group showed that ET treatment was independently associated with : proven sepsis (8% versus 1% respectively, odds ratio (OR) 8.3, 95% confidence interval (CI) 1.7-40.3, $p = 0.009$), leukocytopenia (88% versus 23% respectively, OR 36.0, 95% CI 17.5-73.8, $p < 0.001$), severe thrombocytopenia (platelet count $< 50 \times 10^9$/L) (63% versus 8% respectively, OR 31.4, 95% CI 14.0-70.4, $p < 0.001$), hypocalcemia (22% versus 1% respectively, OR 27.4, 95% CI 5.9-126.8, $p < 0.001$) and hypernatremia (8% versus 0% respectively, $p < 0.001$). Neonatal death did not occur in the group treated with ET.

Conclusion: ET in neonates with HDN is associated with increased risk of sepsis, leukocytopenia, thrombocytopenia, hypocalcemia and hypernatremia.

Introduction

Hemolytic disease of the newborn (HDN) due to red cell alloimmunization may lead to excessive unconjugated hyperbilirubinemia. Neonatal treatment consists of intensive phototherapy and exchange transfusion (ET) to prevent kernicterus. After introduction in the late 1940s[1-3] neonatal treatment with ET became one of the most commonly performed neonatal procedures. However, ET is a high-risk invasive procedure requiring the use of central lines and is associated with a significant rate of adverse events. Several studies have reported on mortality and morbidity rates associated with ET. Although the contemporary mortality rate is reported to be less than 2%, rates of morbidity and ET-related adverse events can reach 74%.[4-11] Reported adverse events include mainly catheter-related complications (malposition, sepsis), complications related to the use of blood products (thromboembolization, graft versus host reactions, infection), metabolic derangements (acidosis, disturbance of serum levels of sodium, calcium, potassium and glucose) and cardio-respiratory reactions (including cardiac arrhythmias, cardiac arrest and apnea).[4-11]

In nearly all previous studies a heterogeneous group of infants with HDN treated with ET was included, varying from red cell alloimmunization to ABO-incompatibility.[4-6,8,10,11] Hemolysis caused by ABO-incompatibility is usually less severe compared to red cell alloimmunization and therefore associated with a reduced rate of neonatal morbidity. Furthermore, different indications for ET were used, including anemia, idiopatic hyperbilirubinemia and metabolic/intrinsic erythrocyte disorders (pyruvate kinase deficiency, glucose-6-phosphate-dehydrogenase deficiency and Gilbert's disease).[4,10,11] In addition, most studies were limited by a relative small number of included patients.[4-11]

The aim of this study was to evaluate the type and rate of complications associated with ET in a large series of neonates with HDN due to red cell alloimmunization exclusively.

Patients and methods

All term and preterm neonates with HDN due to maternal red cell alloimmunization treated with or without ET, admitted to our center between January 2001 and June 2011 were eligible for this retrospective observational study. The Leiden University Medical Center (LUMC) is the national referral center for the management and intrauterine treatment of red cell alloimmunization in the Netherlands. Neonatal outcome in part of this group was reported in previous studies.[12-16]

Guidelines for the management of neonates with HDN admitted to our nursery (including intensive phototherapy and exchange transfusion) have previously been described.[12,13] The guidelines for ET used in our neonatal center were revised 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/h 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.[14] In December 2005 a new guideline of the American Academy of Pediatrics (AAP) with higher bilirubin thresholds for phototherapy and ET was implemented in our nursery.[17] The criteria for ET after December 2005 were: (1) total serum bilirubin above (higher) ET thresholds[17] and/or (2) rise of bilirubin > 0.5 mg/dL/h 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). In our center ET was performed with heparinized blood until December 2000. As of January 2001 heparinized blood was replaced by citrated plasma from a non-transfused male donor, lacking irregular erythrocyte antibodies, which was added to irradiated, leukocyte-depleted ($< 1\times10^6$) and thrombocyte-reduced red cell concentrate, compatible with maternal antibodies. Citrated plasma contains nearly no free calcium and physiologic levels of potassium and glucose, with an increased concentration of sodium (168 mEq/L). Because of the well-known differences in complications between heparinized and citrated blood,[18,19] we started including patients from the moment citrated plasma was used (January 2001).

Primary outcome of this study was the rate of complications during admission in the group treated with ET (ET-group) and without ET (no-ET-group).

An adverse event was defined as any complication that occurred during admission. The following events were recorded (definitions are described between brackets): hypocalcemia (total serum calcium < 8 mg/dL), hypoglycemia (serum glucose < 46.8 mg/dL), hyperkalemia (serum potassium > 6.5 mEq/L), hypokalemia (serum potassium < 3.0 mEq/L), hypernatremia (serum sodium > 150 mEq/L), hyponatremia (serum sodium < 130 mEq/L), metabolic acidosis (requiring treatment with bicarbonate), respiratory failure (requiring respiratory support with continuous positive airway pressure (CPAP) and/or mechanical ventilation), apnea (cessation of respiration for > 20 seconds), pulmonary hemorrhage, cardiac arrest (sudden cessation of heartbeat and cardiac function treated with cardiac resuscitation with either epinephrine and/or chest compressions), hypertension (high blood pressure requiring treatment with antihypertensive medication), hypotension (low blood pressure requiring treatment with intravenous fluids or vasopressors), necrotizing enterocolitis

(classified according to Bell's criteria[20]), proven sepsis (clinical and/or biochemical signs of infection with a positive blood culture), suspected sepsis (clinical and/or biochemical signs of infection without a positive blood culture), disseminated intravascular coagulation (DIC) (requiring treatment with fresh frozen plasma), seizures (clinical evidence of seizure-like activity treated with anti-epileptic medication), leukocytopenia (leukocyte count in the first 24 hours after birth < $9x10^9$/L and after 24 hours < 5×10^9/L)[21], thrombocytopenia (platelet count < 150×10^9/L, defined as severe if platelet count < 50×10^9/L and very severe if platelet count < 20×10^9/L), intraventricular hemorrhage (classified according to Volpe[22]) or other cerebral hemorrhage and neonatal death. In our center, platelet transfusions are given when platelet counts fall below the following thresholds: 1) < 100×10^9/L before planned ET and 2) < 50×10^9/L after ET.

We recorded the following obstetric and neonatal data: type of red cell alloimmunization, number of intrauterine red cell transfusions (IUT), gestational age at birth, birth weight, presence of hydrops at birth, hemoglobin level, reticulocyte count, leukocyte count and bilirubin level at birth, days of admission, occurrence of the above mentioned complications during admission and time of occurrence in relation to ET, number of ETs and presence of umbilical venous catheter.

Data are reported as means and standard deviations (SD) or as medians and interquartile ranges (IQR). 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. A p-value < .05 was considered to indicate statistical significance. Of all statistically significant complications identified with univariate analysis between the ET-group and no-ET-group a multivariate logistic regression analysis was performed to measure the independent effect of ET(s). The results of the logistic regression models were expressed as odds ratios (OR) and 95% confidence intervals (CI). Statistical analysis was performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA).

Results

During this 10-year study, 348 neonates with HDN due to red cell alloimmunization were admitted to our neonatal nursery. We excluded one preterm neonate (born at 29 weeks' gestation) because he died immediately after caesarean section due to severe perinatal asphyxia following unsuccessful IUT. A total of 347 patients were included in this study, 134 (39%) in the group with at least one ET during admission (ET-group) and 213 (61%) in the group without ET (no-ET-group). Baseline characteristics of both groups are summarized in

Table 1 Baseline characteristics in ET-group and no-ET-group

	ET (n = 134)	**no-ET** (n = 213)	**p-value**
Type of red cell alloimmunization			
Rh D - n (%)	122 (91)	138 (65)	< 0.001
Rh c - n (%)	11 (8)	16 (8)	0.813
Kell - n (%)	1 (1)	46 (22)	< 0.001
Other types than Rh D, Rh c or Kell - n (%)	0 (0)	13 (6)	
Neonates treated with IUT - n (%)	99 (74)	141 (66)	0.131
Birth weight - kg[a]	2.9 ± .6	2.9 ± .6	0.591
Gestational age at birth - weeks[b]	36 (36-37)	36 (36-37)	0.247
Male - n(%)	89 (66)	130 (61)	0.311
Hydrops at birth - n (%)	2 (2)	4 (2)	1.000
Hemoglobin level at birth - g/dL[a]	11.6 ± 2.6	12.7 ± 2.9	< 0.001
Reticulocyte count at birth – ‰[b,c]	49 (6.8-83.3)	39 (3-75.5)	0.089
Leukocyte count at birth – 10^9/L[a,d]	14.1 ± 5.6	13.4 ± 5.7	0.270
Thrombocytopenia at birth - n (%)	39 (29)	48 (23)	0.169
Bilirubin level at birth - mg/dL[a]	7.1 ± 3.1	4.8 ± 2.3	< 0.001
Umbilical venous catheter – n (%)	133 (99)	64 (30)	< 0.001
Days of admission[a]	6.6 ± 3.8	6.2 ± 3.9	0.009

[a] Value given as mean ± SD
[b] Value given as median (IQR)
[c] assessed in 78/134 and 149/213 neonates
[d] assessed in 130/134 and 207/213 neonates

Table 1. The mean (± SD) number of ETs in the ET-group was 1.55 ± 1.01 (median 1, range 1-9). Neonates with Rhesus D type of red cell alloimmunization were more likely to require treatment with ET (91% (122/134) versus 65% (138/213), p < 0.001), whereas treatment with ET was only sporadically required in neonates with Kell alloimmunization (1% (1/134) versus 22% (46/213), p < 0.001).

Complications

Detailed information on complications during admission in the ET-group and the no-ET-group is summarized in Table 2.

Univariate logistic regression analysis

Metabolic derangements/complications

Two metabolic complications had a significantly higher incidence in the ET-group than in the no-ET-group: hypocalcemia (22% versus 1%, OR 29.1, 95% CI 6.8-124.5) and hypernatremia (8% versus 0%, OR not calculated, p < 0.001). Four of 31 (13%) neonates with hypocalce-

mia needed calcium replacement therapy and 3 of 11 (27%) needed treatment (additional sodium-free intravenous fluid) for hypernatremia. Severe symptoms of hypernatremia (seizures) did not occur.

Cardio-respiratory complications

No significant differences were seen between the two groups in respiratory support, apneas, cardiac arrest, and hypotension (Table 2). No cases of cardiac rhythm disorders, pulmonary hemorrhage and hypertension (requiring treatment) occurred.

Infectious complications

Proven sepsis occurred significantly more often in the ET-group than in the no-ET-group (8% versus 1%, OR 6.3, 95% CI 1.7-22.9). In the 14 neonates with proven sepsis, bacterial cultures were positive for Staphylococcus aureus in 7/14 (50%), coagulase-negative Staphylococcus in 3/14 (22%), beta-hemolytic Streptococcus in 1/14 (7%), Klebsiella pneumonia in 1/14 (7%), Escherichia coli in 1/14 (7%) and Bacillus cereus in 1/14 (7%). This last patient developed a Bacillus cereus sepsis with brain abscesses after an ET performed through an umbilical venous catheter. This exceptional case has previously been reported.[23]

The rate of leukocytopenia was significantly higher in the ET-group than in the no-ET-group (88% versus 23%, OR 24.7, 95% CI 13.4-45.5). All ET-treated neonates with proven sepsis had leukocytopenia during admission and in 55% (6/11) leukocytopenia occurred after ET.

Umbilical venous catheterization was performed significantly more often in the ET-group than in the no-ET-group (99% versus 30%) (Table 1).

Hematological complications

The rate of thrombocytopenia (platelet count < 150×10^9/L) was significantly higher in the ET-group than in the no-ET-group (99% versus 32%, OR 143.8, 95% CI 34.6-598.6), and this was also true for severe thrombocytopenia and very severe thrombocytopenia (Table 2). Seventy-five of 134 ET-treated neonates (57%, 2 missing values) were treated with at least one platelet transfusion. One near-term neonate with Rhesus D alloimmunization born at 36 weeks' gestation received a platelet transfusion after ET on day one because of a post-ET platelet count of 39×10^9/L. On day 2 a cranial ultrasound showed a hemorrhage in the right parieto-occipital periventricular white matter. This hemorrhage was not seen on antenatal ultrasounds. Magnetic resonance imaging showed no signs of sinus thrombosis and coagulation was normal. At one year of age, the infant had no neurologic sequelae on physical examination. In the no-ET-group 3 neonates had signs of intracerebral hemorrhage on cranial ultrasound and/or MRI of whom one neonate had severe thrombocytopenia for which he received 4 platelet transfusions. This neonate died during admission (see below).

Table 2 Complications during admission in ET-group and no-ET-group

	ET-group	no-ET-group	Univariate analyses		Multivariate analyses	
	n = 134	n = 213	OR (95% CI)	p-value	OR (95% CI)	p-value
Hypocalcemia - n (%)	29 (21.6)	2 (0.9)	29.1 (6.8-124.5)	< 0.001	27.4 (5.9-126.8)	< 0.001
Hypoglycemia - n (%)	14 (10.4)	28 (13.1)		0.453		0.848
Hyperkalemia - n (%)	1 (0.7)	0		0.386		NC
Hypokalemia - n (%)	3 (2.2)	1 (0.5)		0.303		0.220
Hypernatremia - n (%)	11 (8.2)	0	+ ∞	< 0.001	NC	NC
Hyponatremia - n (%)	1 (0.7)	2 (0.9)		1.000		0.949
Metabolic acidosis - n (%)	2 (1.5)	7 (3.3)		0.491		0.103
Respiratory support - n (%)	17 (12.7)	18 (8.5)		0.202		0.425
Apneas - n (%)	7 (5.2)	3 (1.4)		0.050		0.137
Cardiac arrest - n (%)	0	2 (0.9)		0.525		NC
Hypotension - n (%)	2 (1.5)	4 (2)		1.000		0.356
NEC - n (%)	1 (0.7)	2 (1.9)		1.000		1.000
Proven sepsis - n (%)	11 (8.2)	3 (1.4)	6.3 (1.7-22.9)	0.002	8.3 (1.7-40.3)	0.009
Suspected sepsis - n (%)	9 (6.7)	16 (7.5)		0.780		0.466
Leukocytopenia	118 (88.1)	49 (23.0)	24.7 (13.4-45.5)	< 0.001	36.0 (17.5-73.8)	< 0.001
Thrombocytopenia - n (%)	132 (98.5)	67 (31.5)	143.8 (34.6-598.6)	< 0.001	146.9 (34.3-629.1)	< 0.001
Severe - n (%)	85 (63.4)	16 (7.5)	21.4 (11.5-39.7)	< 0.001	31.4 (14.0-70.4)	< 0.001
Very severe - n (%)	14 (10.4)	3 (1.4)	8.2 (2.3-29.0)	0.001	11.5 (2.5-53.2)	0.002
DIC - n (%)	0	1 (0.5)		1.000		0.982
Seizures - n (%)	2 (1.5)	1 (0.5)		0.562		0.931
Death - n (%)	0	1 (0.5)		1.000		NC

ET = exchange transfusion; Respiratory support = continuous positive airway pressure and/or mechanical ventilation; NEC = necrotizing enterocolitis; DIC = disseminated intravascular coagulation; NC = not calculated; OR = odds ratio; CI = confidence interval

Table 3 Complications during admission in Adjusted ET-group and no-ET-group

	Adjusted[a] ET-group	no-ET-group	Univariate analyses		Multivariate analyses	
	n = 134	n = 213	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Hypocalcemia, n (%)	25 (18.7)	2 (0.9)	24.2 (5.6-104.1)	< 0.001	21.9 (4.7-101.7)	< 0.001
Hypernatremia, n (%)	10 (7.5)	0	NC	< 0.001	NC	NC
Proven sepsis, n (%)	8 (6.0)	3 (1.4)	4.4 (1.6-17.1)	0.030	5.30 (1.0-27.1)	0.046
Leukocytopenia, n (%)	91 (70.5)[b]	49 (23.0)	8.0 (4.9-13.2)	< 0.001	9.0 (5.1-15.9)	< 0.001
Thrombocytopenia, n (%)	90 (67.2)	67 (31.5)	4.5 (2.8-7.1)	< 0.001	3.90 (2.4-6.4)	< 0.001
Severe, n (%)	71 (53)	16 (7.5)	14.9 (8.0-27.8)	< 0.001	16.3 (7.8-34.1)	< 0.001
Very severe, n (%)	14 (10.4)	3 (1.4)	8.2 (2.3-29.0)	< 0.001	11.5 (2.5-53.1)	0.002

[a] Only complications which occurred after first ET were analyzed
[b] Assessed in 129/134 neonates

Neonatal mortality

Only one of the 347 neonates died during admission. This neonate from the no-ET-group, born at 30 weeks' gestation, suffered from severe fetal hydrops and died on day 11 due to multiple organ failure including respiratory failure due to respiratory distress syndrome and severe pulmonary hypertension, bilateral intraventricular hemorrhage grade 2 and renal failure.

ET guideline change

To measure the possible effect of ET guideline change[12] on the rate of the previously mentioned complications (Table 2) we performed a sub-analysis of ET treated neonates before and after guideline change. The rates of complications were not significantly different between both groups (data not shown).

Multivariate logistic regression analysis

Complications during entire admission

On multivariate logistic regression analysis we corrected for the following covariates: hemoglobin level at birth, type of red cell alloimmunization, days of admission, and gestational age at birth. We corrected for the first two because of the significant differences at baseline (Table 1) and for the latter because preterm neonates are more susceptible for ET-related complications.[10,24] Since the presence of an umbilical venous catheter and ET are correlated (Spearman correlation coefficient $r = 0.680$, $p = <0.001$), we did not correct for the presence of an umbilical venous catheter. Multivariate regression analysis demonstrated that four complications, i.e. proven sepsis (OR 8.3, 95% CI 1.7-40.3), severe thrombocytopenia (OR 31.4, 95% CI 14.0-70.4), leukocytopenia (OR 36.0, 95% CI 17.5-73.8) and hypocalcemia (OR 27.4, 95% CI 5.9-126.8), had a higher incidence in the ET-group than in the no-ET-group (Table 2). Because none of the neonates in the no-ET-group had hypernatremia, additional multivariate logistic regression analyses could not be performed.

Complications after first ET

In Table 2 all complications during entire admission in both groups are reported. Since our main interest is in ET-related complications, we performed a sub-analysis excluding all complications in the ET-group that were observed before (first) ET (adjusted-ET-group). Results are shown in Table 3.

Discussion

This study demonstrates that treatment with ET in neonates with HDN is associated with an increased risk of sepsis, thrombocytopenia, leukocytopenia, hypocalcemia and hypernatremia. Treatment with ET was not associated with neonatal death in our cohort.

In the last three decades several studies have been published on neonatal morbidity due to treatment with ET.[4-11] One of the known risk factors associated with ET is development of invasive bacterial infections. The reported incidence of ET-related sepsis ranges from 0% to 11%.[6,8,10] The incidence of proven sepsis detected in this study (8%) is in accordance with these previous reports. We found that the independent risk of sepsis was more than eight times higher in the ET-group than in the no-ET-group. The exact cause of the increased risk of infection is not fully understood, but is most probably related to the use of umbilical lines for ET. Umbilical catheters are a well known risk factor for nosocomial infection.[25] Sepsis in the ET-group may also be caused by administration of infected blood products. Although the current risk of transmission of infectious diseases is relatively low, it is not completely negligible.[7,26] Furthermore, ET-related wash out of leukocytes may also play a role in the higher incidence of sepsis in the ET-group, since in double volume ET more than 90% of circulating blood is replaced by leukocyte-depleted donor-blood.[19,26-28] Finally, limited data on leukocytopenia in neonates with HDN due to red cell alloimmunization show that the risk of leukocytopenia is increased in severe Rhesus HDN.[29-32] In this study 86% (12/14) of neonates with proven sepsis had leukocytopenia of whom 11 were treated with ET. In 55% (6/11) leukocytopenia occurred after treatment with ET. In the remaining 45% leukocytopenia might be caused by bone marrow suppression due to increased erythropoiesis.

Another reported risk associated with ET is thrombocytopenia due to the use of a blood product which consists of thrombocyte-free erythrocytes.[18,19,33] Previous studies reported incidences of ET-related thrombocytopenia ranging from 6% to 44%.[4-6,8,10,11] In our study, the incidence of thrombocytopenia ($< 150\times10^9$/L) in the ET-group was much higher, almost all neonates (99%) had low platelet counts and 63% had severe thrombocytopenia (platelets $< 50\times10^9$/L). The differences in incidence can be explained by several factors including methodological differences and differences in study population. We only included neonates with red cell alloimmune HDN which is known to be associated with an increased risk for thrombocytopenia, even without ET.[16,34-36] Because other studies included neonates with ABO-incompatibility, their incidence of thrombocytopenia should be lower. In this study, the risk of severe thrombocytopenia is 21-fold higher in the group treated with ET. Neonatologists must be aware of this potentially devastating complication as massive hemorrhage may arise after ET. Complications can be prevented by prophylactic platelet

transfusion before, during or after ET in case of low platelet counts. In our study, platelet transfusions were administered in 57% of neonates before, during or after ET.

A third known complication of ET is hypocalcemia, resulting from the use of citrated blood which contains almost no free calcium.[18,19,33,37] Previous studies reported incidences of hypocalcemia ranging from 3% to 42%.[4,8,10,11] In our study, 22% of neonates in the ET-group had a serum calcium < 8 mg/dL, and 13% of all hypocalcemic infants needed replacement therapy. We found that treatment with ET was independently associated with an almost 30-fold increased risk of hypocalcemia. If left untreated, hypocalcemia can lead to potentially devastating complications such as seizures and cardiac arrhythmias. It is therefore crucial to measure calcium levels during the ET-procedure and act accordingly.

Another metabolic complication which appears to be related to ET is hypernatremia. Hypernatremia probably results from an increased level of sodium in citrated blood (in our center 168 mEq/L). Only few studies have reported hypernatremia resulting from ET, and the exact incidence is unknown.[38,39] Because hypernatremia can lead to serious complications, we recommend frequent measurements of serum sodium levels during and after ET.

Finally, previous studies have reported that ET may also lead to neonatal death. Neonatal mortality attributable to ET ranges between 0.5% and 2%.[4,8-10] In accordance with our findings, three recent studies reported no neonatal deaths after ET.[5,6,11] However, all these studies (as well as ours) were not powered to detect a difference in neonatal mortality. Differences between the reported rates can be explained by methodological differences such as different sizes of the study cohorts and differences in disease-severity between the cohorts. Neonates included in previous studies were often more premature than the near term-age population in our cohort.[9-11] Another explanation could be that our center is the national referral center for intrauterine treatment of red cell alloimmunization. Consequently nearly all severely affected neonates with HDN due to red cell alloimmunization are born and treated in our center. As a result, ET is a frequently performed and standardized procedure in our unit and part of routine practice. We speculate that this may have contributed to the low level of severe morbidity or mortality in the ET-group.

To our knowledge this is the first large study comparing neonatal complications in a group of infants with red cell alloimmunization treated with ET and a control-group without ET. Nevertheless, the results of this study should be interpreted with care because of the retrospective study design.

In conclusion, sepsis, leukocytopenia, thrombocytopenia, hypernatremia and hypocalcemia are common complications in neonates with HDN due to red cell alloimmunization treated with ET. In experienced hands severe permanent morbidity and mortality rates due to ET-procedures can be reduced to a minimum.

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