Exchange Transfusion for Severe Neonatal Hyperbilirubinemia: 17 Years' Experience from Vojvodina, Serbia

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Abstract This study aimed to evaluate the frequency of the main risk factors for severe neonatal hyperbilirubinemia, to determine the incidence of exchange transfusion (ET) in the Autonomous Province of Vojvodina (the northern part of Serbia) and to describe the experience with ET performed in premature and term infants during the past 17 years. We performed a retrospective data analysis of 398 newborn infants who underwent a double volume ET from 1997 to 2013. During the 17 year study period, a decreasing incidence of ET, expressed per thousand newborns, was observed. A total of 468 double volume ET were performed: 328 (82.4 %) infants had one treatment and 70 (17.6 %) had repeated treatments. A total of 262,830 mLs of blood were transfused, an average of 660 mLs per child. There were 221 male and 177 female infants, with a sex ratio 1.25:1. The frequencies of risk factors for developing hyperbilirubinemia were as follows: (1) 38 % RhD incompatibility; (2) 38 % ABO incompatibility (26 % group A infant of group O mother, 12 % group B infant of group O mother); (3) 7 % low birth weight/preterm birth; (4) 17 % other factors. Risk factors for neurotoxicity were identified in 56.3 % of infants. No deaths or complications were reported arising from the treatment. ABO and Rh incompatibilities were found to be the main risk factors for severe neonatal hyperbilirubinemia in Vojvodina. Exchange transfusion, used as therapy

for severe hyperbilirubinemia, trended downwards over the period of this study.

Keywords Hemolysis · Infant, Newborn · Hyperbilirubinemia, Neonatal · Exchange transfusion, Whole blood · Blood group incompatibility

Abbreviations

EBT	Exchange blood transfusion
HBFN	Hemolytic disease of the fetus and newborn
RBC	Red blood cell
BTIV	Blood Transfusion Institute for Vojvodina
RhD	Rhesus blood group, D antigen
ABO	ABO blood group
ISO	International Organization for Standardization
IAT	Indirect antiglobulin test
DAT	Direct antiglobulin test
BW	Body weight
CPD	Anticoagulant citrate phosphate dextrose
CPDA1	Anticoagulant citrate phosphate dextrose adenine
G6PD	Glucose 6 phosphate dehydrogenase enzyme

Introduction

Exchange transfusion (ET) provides rapid reduction of circulating bilirubin, so it could represent appropriate treatment in many cases of severe hyperbilirubinemia in the neonatal period [1–3]. Treatment involves removal of the infant's blood and simultaneous replacement with compatible donor blood [4, 5]. Immune and non immune-mediated hemolytic disease of the fetus and newborn

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(HDFN) may be accompanied by hyperbilirubinemia requiring exchange transfusion [6]. HDFN, resulting from the maternal alloimmunization against fetal red blood cell (RBC) antigens, inherited from the father and absent in the mother, shows higher rates of bilirubinemia at an earlier stage and has a longer duration than hyperbilirubinemia due to other causes [7–10]. In addition to reducing bilirubin levels ET removes partially hemolyzed RBCs, RBCs coated with antibody and circulating immunoglobulins [6].

The Blood Transfusion Institute of Vojvodina (BTIV) is the reference transfusion institution in the Autonomous Province of Vojvodina (the northern part of Serbia). In order to identify RhD negative mothers who require anti-D prophylaxis as well as detection of existing antibodies potentially harmful for offspring, BTIV performs blood testing of pregnant women. For the purposes of tertiary health care facilities in Vojvodina, BTIV performs pre-transfusion compatibility testing and selection of blood for exchange transfusion and keeps a record of complications related to the treatment. The adoption of computerized records in 1997 and adoption of the ISO 9001 quality management system in 1998 have allowed BTIV to assess the number of ET procedures, indications for treatment, basic demographic data on neonates and their mothers, and the frequency of maternal alloimmunization in Vojvodina. A better knowledge of the indications for ET, and the incidence of ET procedures performed, may be helpful in the management of hyperbilirubinemia in newborn infants [11].

In this study, we aim to evaluate the frequency of the main risk factors for neonatal hyperbilirubinemia, to determine the trend of exchange transfusion in the Autonomous Province of Vojvodina, as well to describe our experiences based on about five hundred exchange transfusions performed in premature and term infants during the past 17 years.

Materials and Methods

Study Design

A retrospective study was conducted to assess the incidence of exchange transfusion in neonates with hyperbilirubinemia from 1997 to 2013 in the northern region of Serbia. Data gathered from transfusion registers and information system of BTIV included: age and sex of the child, ABO blood group and RhD antigen typing of mother and child, the amount and type of blood and blood product required, and the requesting medical institution.

The number of children born in the Autonomous Province of Vojvodina during the study period was obtained

from the Statistical Office of the Republic of Serbia and Institute of Public Health of Serbia [12, 13].

Laboratory Testing

During Pregnancy

Routine laboratory testing of maternal blood samples included: (1) ABO grouping and RhD typing; (2) screening for RBC irregular antibodies by IAT method (indirect antiglobulin test).

Further testing included: (1) Rh phenotyping—for RhD negative women and for the potential father; (2) monitoring of RBC alloantibody development—for pregnant RhD negative women; (3) antibody identification and monitoring of antibody titers—for pregnant women with positive antibody screens.

A comprehensive history of all previous pregnancies was taken (miscarriages, ectopic pregnancy, known alloimmunizations, physical intervention with associated risks to the fetus, previous fetal-maternal hemorrhage and blood transfusion, previous anemic fetus or infant, etc.).

Within the First 24 Hours after Birth

Cord blood testing was performed for children: of group O mothers, of RhD negative mothers, of screening antibody positive mothers. The routine testing included: (1) ABO grouping and RhD typing; (2) DAT (direct antiglobulin test). Further testing for children with DAT positive results included: (1) antibody screening by IAT method; (2) antibody identification if the antibody screening was positive.

All tests were performed using freshly collected venous samples for neonates hospitalized for hyperbilirubinemia and for neonates with neurotoxicity risk factors (gestational age less than 38 weeks, sepsis, asphyxia, acidosis, isoimmune hemolytic anemia, etc.).

All results were sent back to one of two hospitals: either the Institute for Health Protection of Children and Youth of Vojvodina or the Department of Gynecology and Obstetrics of the Clinical Center of Vojvodina.

Indications for Exchange Transfusion

Identification, monitoring and treatment of hyperbilirubinemia in preterm and full-term newborns, including exchange transfusion, were based on national protocols in neonatology, the experience and knowledge of expert clinicians from the Department of Obstetrics and Gynecology and from the Institute of Public Health of Children and Youth of Vojvodina, and followed modern concepts of neonatal-perinatal medicine [14].

All newborns were monitored for the development of jaundice every 8–12 h within 48 to 72 h in the maternity ward. Jaundice was detected by blanching the skin with digital pressure. In all newborns with jaundice total serum bilirubin was measured. The risk of severe hyperbilirubinemia, the age of the newborn in hours, and total bilirubin levels indicated when to initiate phototherapy.

The treatment of hyperbilirubinemia with ET was indicated:

- for healthy term infants within the first 25–48 h after birth with bilirubin levels of 340 $\mu\text{mol/L}$ (19.88 mg/dL); for healthy term infants more than 48 h after birth with bilirubin levels of 430 $\mu\text{mol/L}$ (25.15 mg/dL);
- for term infants with sepsis, acidosis, hypoglycemia, hypoalbuminemia, hypercapnia, hypoxemia, hypothermia, etc., with bilirubin levels of 17–34 $\mu\text{mol/L}$ (0.99–1.99 mg/dL) lower than those previously mentioned (340–430 $\mu\text{mol/L}$ or 19.88–25.15 mg/dL);
- for preterm infants: with birth weight (BW) more than 2000 g at bilirubin levels of 290–310 $\mu\text{mol/L}$ (16.96–18.13 mg/dL); with BW 1501–2000 g at bilirubin levels of 260–290 $\mu\text{mol/L}$ (15.20–16.96 mg/dL); with BW 1001–1500 g at bilirubin levels of 170–260 $\mu\text{mol/L}$ (9.94–15.20 mg/dL); with BW of less than 1000 g at bilirubin levels of 136–170 $\mu\text{mol/L}$ (7.95–9.94 mg/dL).
- in some cases hemolytic disease of the newborn: severe anemia with hemoglobin levels less than 100 g/L; with rapidly rising bilirubin level of greater than 8.5 $\mu\text{mol/L}$ (0.50 mg/dL) per hour; for healthy infants with BW more than 2500 g with increasing unconjugated serum bilirubin levels greater than 340 $\mu\text{mol/L}$ (19.88 mg/dL).
- for septic infants: with BW more than 2500 g at bilirubin levels greater than 306 $\mu\text{mol/L}$ (17.89 mg/dL); with BW 2000–2499 g at bilirubin levels greater than 289 $\mu\text{mol/L}$ (16.90 mg/dL); with BW 1500–1999 g at bilirubin levels greater than 255 $\mu\text{mol/L}$ (14.91 mg/dL); with BW of less than 1250 g at bilirubin levels greater than 153–204 $\mu\text{mol/L}$ (8.95–11.93 mg/dL).

Selection of Blood for Exchange Transfusion

Product selection, compatibility testing and administration of blood were done according to the defined written procedures of the quality management system of BTIV. Modified whole blood or leukocyte-depleted red blood in CPD or CPDA-1 anticoagulant-preservative solution, stored up to 5 days after collection, reconstituted with fresh frozen plasma to reduce hematocrit to 50–60 %, was used for ET. All units were crossmatch compatible with the child's serum using IAT method by gel technique on

commercial LISS/Coombs cards (DiaMed AG 1785 Cresier, Switzerland). The volume of blood was calculated as twice the blood volume of the neonates (2 times 85–90 mL/kg body weight). In the case of ABO incompatibility, group O, Rh specific RBCs were reconstituted with group AB fresh frozen plasma, free of clinically significant irregular blood group antibodies. In the case of RhD incompatibility, ABO compatible, RhD negative RBCs were used. When other red blood cell alloantibodies were present, the red cell units selected for transfusion were ABO and Rh compatible, and negative for antigens corresponding to the alloantibody specificities.

Exchange Transfusion Complications

BTIV had established process and procedure for documentation, reporting, evaluation, and follow-up of all adverse reactions. Although the computer data system of the BTIV is not linked to that of the aforementioned clinics, physicians at these clinics reported any adverse reaction to the transfusion of blood or blood products to us on a standard form known as the “Transfusion Reaction Report Form”.

The overall risk of treatment can be divided into individual risks due to: (1) the cause of hyperbilirubinemia; (2) performing the procedure; (3) transfusion of blood products; (4) human error. Potential complications included cardiac and respiratory disorders, shock due to bleeding or inadequate replacement of blood, infection, blood clots leading to occlusion of the catheter or impairment of blood flow to organs, changes in the composition of the blood (high or low potassium, low calcium, low glucose, changes of pH), and the rare but serious complications of air embolism, portal hypertension, and necrotizing enterocolitis.

Results

A retrospective data analysis of 398 newborn infants who underwent a double blood volume exchange for treatment of hyperbilirubinemia was performed over the period 1997–2013. During the 17 year study period, a total of 468 ET procedures was performed: 328 (82.4 %) infants had one treatment and 70 (17.6 %) infants had repeated treatments. A total of 262,830 mLs of blood were transfused, an average of 660 mLs per child.

Trend analysis of the annual number of ET procedures due to severe neonatal hyperbilirubinemia is given in Fig. 1.

A group of 398 neonates included 221 male and 177 female infants, demonstrating a sex ratio of 1.25:1 males to females.

The frequencies of risk factors for developing hyperbilirubinemia were as follows: (1) 38 % (150 infants) RhD incompatibility; (2) 38 % (150 infants) ABO incompatibility (26 % (103) group A infant of group O mother, 12 % (47) group B infants of group O mother); (3) 7 % (28 infants) low birth weight/preterm birth; (4) 17 % (70 infants) other factors. The main risk factors for severe neonatal hyperbilirubinemia in the Autonomous Province of Vojvodina during 1997–2013 are shown in Fig. 2.

The number of neonates who underwent ET during two time periods was compared: 273 infants who underwent ET

between 1997 and 2004 and 125 infants who underwent ET between 2005 and 2013 (relation 1: 0.46).

Out of a total of 398 neonates, 174 (43.7 %) underwent exchange transfusion in the Department of Obstetrics and Gynecology of the Clinical Center of Vojvodina, while 224 (56.3 %) underwent exchange transfusion in the Pediatric Clinic of the Institute for Health Protection of Children and Youth of Vojvodina. Of these 224, 110 (27.6 %) were treated in the Department of Intensive Care and Therapy, 86 (21.6 %) in the Department of Neonatology, and 28 (7.1 %) in the Department of Premature Infants. During the

Fig. 1 Trend analysis of the annual number of ET procedures due to severe neonatal hyperbilirubinemia

Fig. 2 The main risk factors for severe neonatal hyperbilirubinemia in the Autonomous Province of Vojvodina during 1997–2013

research period there were no reports of posttransfusion complications in neonates related to treatment.

Table 1 presents statistical data for the Autonomous Province of Vojvodina involving the number of live births as well as the number of newborns who underwent ET in the period 1997–2013.

Discussion

This retrospective study presents the high frequency of severe neonatal hyperbilirubinemia which required ET in population of Vojvodina between 1997 and 2013. Mother-fetus ABO and Rh incompatibilities were found to be the most common causes of severe neonatal hyperbilirubinemia. A decrease in the number of exchange transfusion performed annually for hyperbilirubinemia is revealed during the seventeen-year time period covered by the study.

Treatment of severe neonatal hyperbilirubinemia by ET was introduced in the early 1950s [15]. RhD incompatibility was one of the most common risk factor for severe hyperbilirubinemia in newborn infants, requiring ET in a range of 20 % to more than 70 %. The majority (88 %) of treatments were performed in the first twelve hours after birth. After the Division of Neonatology, Department of Pediatrics, Leiden University Medical Centre, in the Netherlands, adopted the more-restrictive guidelines from the American Academy of Pediatrics for the treatment of

hyperbilirubinemia in 2005, their use of ET decreased to less than 20 % [16].

The data of this study are consistent with published data because it was found that maternal alloimmunization on fetal antigens inherited from the father was a major cause of neonatal hyperbilirubinemia which required ET. The majority (76 %) of ET procedures were performed because of acute hemolysis due to ABO and RhD incompatibilities. Low birth weight/preterm birth were the reason for 7 % of the cases of severe hyperbilirubinemia, 17 % were caused by other risk factors. A review of the literature enumerates other reasons for severe jaundice such as hereditary spherocytosis, urinary tract infections, hypothyroidism, hemolysis due to blood subgroup incompatibilities, pyruvate kinase enzyme deficiency, hemoglobinopathies and subdural hematoma [17].

Similar findings were observed in a study conducted in Turkey from 2002 to 2008. This study showed that the leading causes of hyperbilirubinemia, among 116 neonates who required ET were ABO and Rh incompatibilities (41 %). The Turkish researchers found unknown etiology in 40 % of the newborns. The results of our study are consistent with literature reporting a frequency of newborn infants with undetermined etiology of hyperbilirubinemia ranging from 17 to 37 % [18].

Other studies have reported a significant share (from 31.5 to 34.4 %) of glucose-6-phosphate dehydrogenase (G6PD) deficiency in the distribution of neonatal kernicterus [19]. A deficit of G6PD is often associated with severe hyperbilirubinemia requiring ET in newborns with lower concentrations of bilirubin. A limitation of our study is the lack of data about the role of G6PD deficiency in the development of severe hyperbilirubinemia in newborns. This indicates a need for screening for G6PD in neonates.

It is reported that infants who left the hospital after body weight loss of ten percent or more, before their level of bilirubin was normalized, have a high probability of developing hyperbilirubinemia and kernicterus, as well as the possibility of rehospitalization [20]. Of infants in our study hospitalized for hyperbilirubinemia at the Pediatric Clinic of The Institute for Health Protection of Children and Youth of Vojvodina, 56.3 % had one or more risk factors for associated neurotoxicity.

To date the BTIV is the only institution in Vojvodina which keeps a record of the number of ET procedures. Our data in this study derives from the BTIV's records. The study identifies a large number of ET procedures performed, and shows a decreasing trend of ET. The Protocols in neonatology from the Institute of Neonatology in Belgrade, Serbia (with the more-restrictive guidelines for the treatment of hyperbilirubinemia), were published in 2003 so that the year 2004 was used as a cut point to differentiate

Table 1 The number of newborn who underwent ET per 1000 live births in Vojvodina

Year	Number of live births (N)	Number of newborn underwent ET (n)	1000 n/N (%)
1997	20,645	54	2.6
1998	19,894	31	1.6
1999	18,686	44	2.4
2000	18,792	22	1.2
2001	20,145	40	2.0
2002	20,030	36	1.8
2003	20,381	28	1.4
2004	20,206	18	0.9
2005	19,058	18	0.9
2006	19,102	8	0.4
2007	18,380	10	0.5
2008	18,339	24	1.3
2009	18,590	27	1.5
2010	18,145	5	0.3
2011	17,410	14	0.8
2012	16,667	11	0.7
2013	16,600	8	0.5
Total	321,070	398	1.2

two time periods in the study, in order to explain the ET downward trend.

As there was no reporting of complications it leaves the possibility of extensive practical experience based on a large number of performed procedure. Despite increased experience with ET, as well as the improvement in the procedure, exchange transfusion remains invasive procedure with a high risk of side effects. The morbidity rates (bacteremia, necrotizing enterocolitis, catheter-related complications) associated with exchange transfusion can reach 24 % [21]. Short term complications such as hypocalcemia, hypoglycemia, apnea and bradycardia with cyanosis, can be occur with a frequency of 5.2 to 17 % [22].

The leading cause of death related to process ET is cardiovascular collapse that occurs as a complication of necrotizing enterocolitis, sepsis and pulmonary hemorrhage [23]. The mortality rate ranges from 0.3 to 1.5 %.

Throughout the observation period, there were no reports of ET-related deaths or serious complications in neonates. Considering two facts, that during the research period there were no reports of posttransfusion complications in neonates related to treatment and that 0 % rate of complications is unusual, it can be concluded that the system to monitor complications was not in BTIV hands so that complication rate cannot be surmised from our study.

The prevention and management of hyperbilirubinemia in newborn infants is important in the prevention of development of severe hyperbilirubinemia and acute bilirubin encephalopathy or kernicterus. Progress in laboratory diagnosis has brought undoubted benefits in terms of the detection of mothers with an increased risk of having children with hemolysis, as well as in the early diagnosis and management of hemolytic disease of the fetus and newborn [24]. Our study presents an algorithm for identifying alloimmunized pregnant women in the BTIV, testing of infants and treating with ET in order to contribute to the prevention, detection and management of hyperbilirubinemia in neonates. Early diagnosis is particularly important in neonates with associated risks. The introduction of the diagnostic technique of non-invasive fetal RhD genotyping in maternal blood serum would help in achieving this task.

Despite the declining frequency of ET there is a need for more efficient management of hyperbilirubinemia. Improvement in clinical management protocols and better availability of phototherapy could help in achieving this goal.

The manuscript does not contain clinical studies or patient data.

Conflict of interest None to declare.

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