

Adverse events related to exchange transfusion in newborn infants with hemolytic disease: ten years of experience

Eventos adversos associados à exsanguíneotransfusão na doença hemolítica perinatal: experiência de dez anos

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ABSTRACT

Objective: To determine the incidence of adverse events associated with exchange-transfusions performed during the past ten years and to evaluate if there is association between the severity of patient's clinical condition before the procedure and the incidence of adverse events.

Methods: All infants admitted to treat hemolytic disease secondary to Rhesus Alloimmunization in the Neonatal Intensive Care Unit were enrolled in the study. Patients were divided into two groups: Group 1, neonates admitted solely for asymptomatic hyperbilirubinemia before the exchange transfusion; Group 2, neonates with other medical conditions besides the hemolytic jaundice. Incidence of adverse events was determined, as well as the relative risk of each adverse event.

Results: 300 newborn infants with Rh hemolytic jaundice were studied. A total of 143 patients underwent 207 exchange transfusions. The rate of increase in the serum bilirubin levels ($>0,5\text{mg/dL/hour}$) was the main indication for exchange transfusion. Adverse events occurred in 22.7% of the cases and the mortality rate was 0.7%. The majority of adverse events were asymptomatic, and low platelet count was the most frequent one. The incidence of serious adverse events (bradycardia or heart arrhythmias and thrombocytopenia) was 2.1 times higher in Group 2 than in Group 1 (RR: 2.1; CI: 95% 1.3-3.4). There was one death during the study period associated to the procedure.

Conclusions: Although exchange transfusion is a frequent procedure for treating severe neonatal hyperbilirubinemia,

the incidence of adverse events is high, especially if patients' clinical condition is unstable before the procedure.

Key-words: blood transfusion; newborn; anemia, hemolytic; Rh isoimmunization.

RESUMO

Objetivo: Determinar a incidência dos eventos adversos atribuíveis à exsanguíneotransfusão ocorridos em uma Unidade de Terapia Intensiva Neonatal (UTIN) e sua associação com a gravidade clínica do paciente.

Métodos: Foram incluídos no estudo todos os recém-nascidos internados com diagnóstico de doença hemolítica perinatal por aloimunização Rh em uma unidade neonatal no período de dez anos. Os pacientes foram separados em dois grupos de acordo com o quadro clínico anterior à exsanguíneotransfusão e calculou-se o risco relativo para cada evento adverso entre os grupos.

Resultados: 300 recém-nascidos foram internados com diagnóstico de anemia hemolítica por aloimunização Rh durante o período do estudo. Desses, 143 foram submetidos a 207 exsanguíneotransfusões, sendo que 93 (65%) realizaram apenas um procedimento. A principal indicação da exsanguíneotransfusão foi a velocidade de hemólise (57%). A incidência de eventos adversos foi 22,7% e a mortalidade associada ao procedimento ocorreu em 0,7% dos pacientes. Os eventos adversos, em sua maioria, foram assintomáticos e o mais comum foi a plaquetopenia. Os pacientes do Grupo 2, que apresen-

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tarem icterícia associada a outros agravos clínicos antes do procedimento, tiveram um risco 2,1 vezes maior de apresentar eventos adversos graves (RR: 2,1; IC 95%: 1,3-3,4). Houve apenas um óbito relacionado ao procedimento no período.

Conclusões: Apesar de a exsanguíneotransfusão ser um procedimento frequentemente utilizado em casos de hiperbilirrubinemia grave, é alta a incidência de eventos adversos a ela relacionada, principalmente se a condição clínica do paciente for instável antes do procedimento.

Palavras-chave: transfusão de sangue; recém-nascido; anemia hemolítica; assistência perinatal; isoimunização Rh.

Introduction

Exchange transfusion (EXT) was the first successful treatment to be introduced for severe neonatal jaundice. Although EXT is considered to be a safe procedure, it is not risk free, and mortality rates vary from 0.5 to 3.3%⁽¹⁻⁴⁾.

Over recent years, the need for this procedure has been reduced to the extent that new techniques have been introduced for prophylactic and therapeutic management of Rh alloimmunization. The introduction of anti-Rh(D) specific immunoglobulin, intrauterine transfusions, prenatal monitoring, high-intensity phototherapies and, more recently, the use of nonspecific human immunoglobulin have made considerable contributions to reducing the indications for EXT⁽⁵⁻⁹⁾.

The level of bilirubin concentration at which EXT should be indicated remains the subject of disagreement, since the incidence of bilirubin encephalopathy also depends on other variables such as gestational age, the presence or absence of hemolysis and the newborn's clinical status. Current recommendations for performing EXT are based on seeking a balance between the risks of encephalopathy and the adverse events related to the procedure⁽¹⁰⁾.

In this context, the objective of this study was to determine the incidence of adverse events related to EXT carried out in a neonatal intensive care unit and their association with the clinical status of newborns prior to the procedure.

Methods

This was a retrospective cohort study based on data from newborn infants admitted to the neonatal unit at Instituto Fernandes Figueira, Rio de Janeiro, and treated with EXT

for a diagnosis of perinatal hemolytic disease due to anti-Rh(D) antibodies, during the last 10 years (1997-2007). The study was approved by the Human Research Ethics Committee at Instituto Fernandes Figueira, Fundação Instituto Oswaldo Cruz.

The newborn infants were identified on the neonatal unit's computerized database, on the hemotherapy department's database and through the analysis of records of both mothers and neonates admitted during the study period. Patients were excluded if their hemolytic disease had causes other than Rhesus alloimmunization or if they had not been born at the unit.

EXT procedures were performed at the unit's neonatal intensive care unit by the treating medical team; newborn infants' heart rate and hemoglobin saturation were monitored. The umbilical vein was the only access employed for the procedure, and the volume of blood used in the exchange corresponded to twice the patient's blood volume. In all cases, reconstituted whole blood supplied by Hemocentro do Rio de Janeiro (HEMORIO) was used less than even days after collection, stored with citrate-phosphate-dextrose. The EXT technique did not change over the ten years studied. All patients were submitted to phototherapy before the procedure.

The patients' medical records were analyzed and the patients were classified into Group 1 or Group 2 according to the criteria used by Jackson⁽¹⁰⁾. Alloimmunized newborn infants who had been admitted with hyperbilirubinemia alone prior to undergoing EXT were allocated to Group 1; alloimmunized newborn infants requiring oxygen therapy or presenting heart failure, severe anemia (hematocrit $\leq 25\%$), five-minute Apgar < 7 or hydrops fetalis were allocated to Group 2.

The following were considered to be adverse events associated with EXT^(10,11), as long as they occurred during or up to 48 hours after the procedure:

- Metabolic disorders: Metabolic acidosis (bicarbonate < 16 mmol/L), hyperkalemia (potassium > 6 mEq/dL), hypocalcemia (serum calcium < 8 mEq/dL or ionized calcium < 3 mEq/dL), hypoglycemia (glycemia < 40 mg/dL), and hyponatremia (serum sodium < 130 mEq/dL).
- Thrombocytopenia: platelet counts reaching values $< 50,000$ mcL after EXT.
- Sepsis: patients admitted with a negative blood culture who developed a clinical status compatible with infection and a positive blood culture.
- Cardiorespiratory decompensation: abnormal cardiac (tachycardia, bradycardia or arrhythmia) and respiratory

function (tachydyspnea or apnea) or hypotension during or soon after EXT. Perfusion disorders occurring during or soon after the procedure were also included in this group.

- Death occurring during or up to 6 hours after the procedure, according to the criteria used by Boggs⁽⁴⁾.

Statistical analysis was carried out using Epi-Info 2000 (CDC, Atlanta, USA). Fisher's exact test or the chi-square test were used to compare proportions of adverse events between the two groups. Student's *t* test and nonparametric tests were used to compare means and medians between groups. Analysis of the associations between EXT and adverse events was carried out using confidence intervals (95% CI) and relative risk (RR).

Results

During the study period, a total of 300 patients with perinatal hemolytic disease were admitted to the neonatal unit, and 143 of them required EXT. Between 1997 and 2001, 79 newborn infants (55%) underwent EXT; over the following five years, 64 (45%) were submitted to the procedure. Of the 143 newborn infants requiring EXT, 90 (63%) were in Group 1 and 53 (37%) in Group 2. Table 1 shows characteristics of the study population according to their clinical status. It is interesting to observe that 69 (48%) of the 143 newborn infants had undergone intrauterine transfusion: 38 in the healthy group (Group 1) and 31 in the symptomatic group (Group 2).

The total number of EXT procedures carried out was 207: 118 in Group 1 and 89 in Group 2. The most common indications for EXT were: increased bilirubin concentrations $>0.5\text{mg/dL/hour}$ (57% of the patients), bilirubin $>20\text{mg/dL}$ at any age (20%), cord blood bilirubin $>4\text{mg/dL}$ (12%) or cord blood hematocrit levels $<30\%$ (11%). Of the 143 newborn infants studied, 93 (65%) required one single EXT, and 50 (35%) required two or more procedures. The incidence of adverse events in the 207 procedures was 22.7% and was significantly higher among those who underwent more than one EXT ($p<0.01$). Forty-seven (33%) of the 143 neonates submitted to EXT experienced adverse events, including one death. Twenty-three (46%) of the 50 neonates requiring two or more EXT suffered at least one adverse event, compared with 24 (25%) of the 93 newborn infants who received just one EXT.

Taking all 143 patients as a single set, the most common adverse event among patients submitted to EXT was thrombocytopenia (11%), followed by metabolic disorders (5%). The risk of adverse events associated with EXT was significantly greater in Group 2 (RR: 2.1; 95% CI: 1.3-3.3).

The relative risks of adverse events according to the patients' clinical condition prior to EXT are shown in Table 2. Newborn infants in Group 2 showed a 2.3 greater risk for developing thrombocytopenia than those in Group 1 (95% CI: 1.15-4.6). Fifteen patients in Group 2 developed thrombocytopenia, and 67% of these required concentrated platelet transfusions. In Group 1, none of the patients pre-

Table 1 – Sample characteristics

	Group 1 (n=90)	Group 2 (n=53)	<i>p</i>
Gestational age (weeks)	36.3±1.9	34.7±3.1	NS
Birth weight (g)	2757±74	2461±574	<0.05
5-minute Apgar <7	0	15 (28%)	<0.05

NS: non-significative

Table 2 – Relative risk of adverse events affecting newborns according to clinical condition prior to EXT

Adverse events	Group 1 (n=90)	Group 2 (n=53)	RR	95% CI	<i>p</i>
Thrombocytopenia	11 (12%)	15 (30%)	2.32	1.15-4.66	<0.01
Metabolic disorders	3 (3%)	4 (8%)	2.26	0.53-9.73	>0.05
Cardiorespiratory decompensation	2 (2%)	5 (10%)	4.25	0.85-21.12	>0.05
Confirmed sepsis	4 (4%)	2 (4%)	0.85	0.16-4.48	>0.05

RR: relative risk; CI: confidence interval.

senting thrombocytopenia after the EXT required concentrated platelet transfusions.

Seven patients developed metabolic disorders: hypocalcemia in four cases, hypoglycemia in two, and hyponatremia in one. Their laboratory test results for ions and glucose had been normal before the procedure.

The only death associated with EXT occurring among the 143 patients (0.7%) during the study period was a baby in Group 1 who suffered arrhythmia and cardiac arrest during the procedure. Analysis of blood samples from the newborn and from the blood bag did not detect any abnormalities that could explain the outcome.

Discussion

Although the number of cases of hemolytic disease secondary to Rh alloimmunization has reduced in developed countries, in Brazil its continued high incidence is probably a result of failure to prevent the disease. In the state of Rio de Janeiro, a high prevalence of alloimmunization to the Rh(D) antigen is observed among donors to blood banks, providing evidence that prevention strategies are inefficient⁽¹²⁾. The main deficiencies associated with prophylaxis are: failure to recognize sensitization events during pregnancy; failure to administer anti-D immunoglobulin; and sensitization due to spontaneous and clinically-silent episodes of fetomaternal hemorrhage⁽¹³⁾.

The conventional treatment of alloimmunized newborns includes phototherapy and EXT. The latter is the only therapeutic modality capable of removing anti-Rh antibodies and sensitized red blood cells. While the benefits of EXT in Rh hemolytic disease are well established, the risks remain high: reported mortality rates associated with the procedure are around 2% in the literature; in this study, the rate was 0.7%^(1,2,5).

Adverse events are defined as any undesirable medical event whatsoever, which may be present during treatment with a pharmaceutical agent, without necessarily having a causal relationship with that treatment. All adverse events can be considered as suspected adverse reactions to a medication⁽¹⁴⁾. In this study, the technology under study was EXT, and the adverse events analyzed were those oc-

curing after the procedure and potentially associated with it. Nevertheless, it is not possible to assure that all clinical conditions analyzed as EXT-related adverse events in the present study were undoubtedly caused by it, since the majority of patients affected presented an unstable clinical status prior to EXT.

The frequency of EXT-related adverse events varies in different studies (15 to 74%), depending on the definition of adverse event taken into consideration and on the severity of the newborn infants studied⁽¹⁰⁻¹²⁾. In our study, a 23% incidence of adverse events was observed in 207 procedures. These events affected 38% of the newborn infants with hemolytic disease enrolled in the study. Jackson observed a greater frequency (62%) of patients suffering adverse events after EXT, although the categories used to define adverse events were different⁽¹⁰⁾. In 2002, Patra et al. also observed a higher incidence (74% of the procedures involved some type of adverse event), but their population had a more severe profile. Moreover, those authors considered as EXT-related adverse events any complication, from technical difficulties changing the blood to cases suspected sepsis, that occurred during the 7 days following the procedure, which was not the case in our study. The most common adverse event in that study was also thrombocytopenia⁽¹¹⁾. Sampavat observed a frequency of adverse events of 15%; in 67% of the patients affected, the events were related to infectious complications⁽¹⁵⁾.

Although the methodologies employed by different studies present variations, in all of them the most frequent adverse events were asymptomatic. The clinical condition of patients before the procedure and the severity of their hemolytic disease presented a statistically significant association with the incidence of these events^(10,11,14), which is in line with our results.

We conclude that although EXT is a common procedure in the management of cases of severe hyperbilirubinemia, the frequency of associated adverse events is high. Whenever the performance of EXT is considered, a thorough evaluation of the patient's clinical condition should be carried out, taking account of the risks and benefits of the procedure. In addition, EXT should only be carried out in institutions that have teams prepared to identify and treat possible adverse events.

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