Benefits of Delayed Cord Clamping in Red Blood Cell Alloimmunization

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BACKGROUND AND OBJECTIVE: Several studies have shown the benefits of delayed cord clamping (DCC) in preterm and in healthy newborns at short and long term. Our objective was to evaluate the potentials benefits and risks of DCC in red cell alloimmunization.

METHODS: This was a comparative before/after study of all living born neonates followed after fetal anemia requiring in utero transfusion. DCC was defined as cord clamping 30 seconds after birth.

RESULTS: We included a continuous series of 72 neonates: 36 without DDC (group 1) and 36 with DDC (group 2). Hemoglobin at birth was lower in group 1 (10.2 vs 13.4 g/dL, P = .0003); 7 (25%) neonates in group 1 vs 24 (70.6%) in group 2 had no anemia at birth (P = .004). The rate of transfusion was similar between the 2 groups. Postnatal exchange transfusions were more likely performed in the group without DCC than in the group with DCC (47.2% vs 19.4%, P = .0124). Delay between birth and first transfusion was higher in group 2 (0 [0–13] vs 1 [0–21], P = .0274). The maximum level of bilirubin, the rate of intensive phototherapy, and the total duration of phototherapy were similar in the 2 groups.

CONCLUSIONS: This study highlights a significant benefit of DCC in anemia secondary to red blood cell alloimmunization with a resulting decreased postnatal exchange transfusion needs, an improvement in the hemoglobin level at birth and longer delay between birth and first transfusion with no severe hyperbilirubinemia.

WHAT'S KNOWN ON THIS SUBJECT: Delayed cord clamping in preterm birth and in healthy newborns allows a significant increase in hematocrit and hemoglobin at birth, and in ferritin level leading to a significant decrease in the risk of anemia in the first months of life.

WHAT THIS STUDY ADDS: This is the first study evaluating delayed cord clamping in red cell alloimmunization. It allows an increase of hemoglobin at birth, longer delay before first neonatal transfusion and a diminution of exchange transfusion without more neonatal complication due to hyperbilirubinemia.
Immune hemolytic disease of the newborn is responsible for neonatal anemia and jaundice. Therapeutic support of this pathology requires, according to the degree of severity, phototherapy (PT), and/or exchange transfusion (ET), and/or blood transfusions, and/or immunoglobulin infusion.1–3

Approximately 25% to 60% of the total blood volume of fetal placental circulation (54–160 mL) and 60% of fetal red blood cells is found in the placental circulation.4,5 This blood is rich in hematopoietic stem cells.6 At birth, delayed cord clamping (DCC) allows placental blood transfusion, which can represent up to one-quarter to one-third of the total blood volume of the newborn at term.5 Several trials and meta-analyses have studied the benefits of DCC versus early cord clamping.7–17 In preterm infants, Rabe et al16 showed, in a meta-analysis of 10 studies describing a total of 454 preterm infants, that major benefits of the DCC were higher circulating blood volume during the first 24 hours of life, less need for blood transfusions (P = .004), and less incidence of intraventricular hemorrhage (P = .002). Recently, Chiruvolu et al18 confirmed those results with a reduction of early red blood cell transfusion in the DCC group compared with a historical cohort (13.3% vs 33%) (odds ratio 0.11, 0.03–0.41). In healthy newborns, after delayed clamping, it was observed at birth a significant increase in hematocrit and hemoglobin (Hb) in the physiologic range, and an increase in ferritin level leading to a significant decrease in the risk of anemia in the first months of life.9,12 At 4 years of age, DCC compared with early cord clamping improved scores in the fine-motor and social domains, especially in boys.19 However, DCC has never been studied in case of alloimmunization. Our hypothesis is that DCC allows a higher rate of Hb at birth allowing less need for transfusions (blood transfusions or ET), which can decrease neonatal morbidity linked to those procedures. However, reserves concerning DCC in red blood cell alloimmunization are the risks of overloading the newborn with additional incompatible red blood cells, leading to increased levels of bilirubin.

In 2009, we began DCC in cases of red cell alloimmunization with a history of utero transfusions. Our objective was to evaluate the potentials benefits and risks of DCC in a comparative before/after study.

**METHODS**

This is a comparative before/after study, from January 2001 to December 2014, of all living neonates followed after fetal anemia requiring in utero transfusion (IUT). We included a continuous series of neonates with DCC and compared it with a similar continuous series of historic cohort with immediate cord clamping (ICC). Ethical approval was granted by the French Ethics Committee of research in Obstetrics and Gynecology (CEROG OBS 2012-02-04).

In the first few years of the study, IUT was indicated whenever the optical index at 450 nm (OD450) fell in zone III of the Liley diagram.20 This technique was progressively replaced by the middle cerebral artery peak systolic velocity (MCA PSV). Fetal anemia was defined as MCA PSV greater than 1.5 to 1.55 MoM.21 Technical realization of IUT was the same as previously described.22 IUT was performed until the 34th week of gestation. Beyond this age, fetal extraction was discussed with the perinatal specialists.

In our center, we have a systematic policy of DCC in premature infants born before 34 weeks of gestation, in agreement with the recommendations of the European Resuscitation Council.23 Since 2009, we have extended our DCC protocol to include cases of red cell alloimmunization with a history of utero transfusions. We have defined DCC as cord clamping 30 seconds after birth.

Hb level was evaluated during the first hour of life. Our neonatal management was similar as previously described.24 Phototherapy (PT) was administered with 2 devices (Tunnel MIDPREMA, Tours, France, and NATUS NeoBlue, Natus Medical Inc, San Carlos, CA). During the study period, the neonatal protocol changed and PT was systematically done in case of alloimmunization since. ET was performed with double-volume transfusion (160 mL/kg) using irradiated and leukocyte-depleted erythrocytes and our criteria for ET were bilirubin level at birth >3.5 mg/dL or bilirubin levels above threshold in combination with failure of PT. Indication for red blood cell transfusion was Hb level at birth <10 g/dL or if clinical symptoms of anemia were present.

Data concerning obstetric history, antenatal management, and neonatal outcome until the discharge from the NICU were collected.

**Statistics**

We compared 2 groups: 1 without DCC (ICC group) during the first period of the study (January 2001–June 2009) and 1 with DCC (June 2009–December 2014). The primary outcome was the need of blood transfusion or ET after birth. Secondary outcomes were Hb level at birth, free serum bilirubin postnatal maximum levels, duration of PT, transfer rate to the neonatal unit, and duration of initial hospitalization. Qualitative variables are expressed as frequency (percentage) and quantitative variables as mean ± SD or median (range) in case of non-Gaussian distribution (normality of distribution was checked graphically...
and by using the Shapiro–Wilk test). Comparisons between the 2 groups were made using the $\chi^2$ test (or Fisher exact test when expected cell frequency was <5) for qualitative variables and the Student $t$ test (or Mann-Whitney $U$ test for non-Gaussian distribution) for quantitative variables.

Statistical testing was done at the 2-tailed $\alpha$ level of 0.05. Data were analyzed by using the SAS software package, release 9.4 (SAS Institute, Inc, Cary, NC).

RESULTS

We included a continuous series of 72 neonates: 36 with ICC and 36 with DCC. Cord clamping was done in all neonates of group DCC. Characteristics of the population are summarized in Table 1. The main antibody was Rhesus D (80.6% in group 1 and 72.2% in group 2). There were no differences between the 2 groups regarding the age, the gestity, and the rate of hydrops fetalis.

Gestational age and Hb at first IUT were comparable (Table 2). Antenatal management was similar during the periods with comparable delay between last IUT and birth, and same rate of MCA PSV $\geq$1.5 MoM before delivery. We observed 5 emergency cesarean deliveries (4 in ICC group and 1 in DCC group) secondary to bradycardia during the IUT. Cord clamping was done before resuscitation by the pediatrician.

Gestational age at birth and birth weight were lower in the ICC group (Table 3). Hemoglobin at birth was higher in the ICC group (5.6 $\pm$ 2.4 vs 6.7 $\pm$ 2.5 g/dL, $P = .0003$); 7 (25%) neonates in the ICC group versus 24 (70.6%) in the DCC group had no anemia at birth (Hb $>$12 g/dL) ($P = .004$).

The rate of neonatal transfusion was similar between the 2 groups.

Postnatal ETs were more likely performed in the ICC group than in the DCC group (47.2% vs 19.4%, $P = .0124$). The delay between birth and first transfusion was higher in DCC group (0 [0–13] vs 1 [0–21] day, $P = .0274$). The maximum level of bilirubin was comparable between the 2 groups; 83.3% of neonates required PT (intensive or not) in ICC group versus 97.1% in DCC group. The rate of intensive PT and the total duration of PT were similar in the 2 groups ($P = .49$ and $P = .66$).

No neonatal death was observed during the study period.

DISCUSSION

To our knowledge, this is the first description of DCC in moderate or severe immune anemia since red blood cell alloimmunization was excluded from all previous studies. Our study demonstrated a significant benefit of DCC in immune anemia managed by IUT. We observed a significant increase in Hb levels at birth, a longer delay between birth and first transfusion, and lower rate of intensive PT.

### Table 1 Population

<table>
<thead>
<tr>
<th>Group</th>
<th>ICC, $n = 36$</th>
<th>DCC, $n = 36$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>30 (22–40)</td>
<td>35 (20–41)</td>
</tr>
<tr>
<td>Gestity</td>
<td>3 (1–6)</td>
<td>3 (1–6)</td>
</tr>
<tr>
<td>Maternel Ab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RH1 (RhD)</td>
<td>29 (80.6)</td>
<td>26 (72.2)</td>
</tr>
<tr>
<td>RH3 (Anti-E)</td>
<td>2 (5.6)</td>
<td>1 (2.8)</td>
</tr>
<tr>
<td>RH4 (Anti-c)</td>
<td>1 (2.8)</td>
<td>3 (8.3)</td>
</tr>
<tr>
<td>Kell</td>
<td>4 (11.1)</td>
<td>6 (16.7)</td>
</tr>
<tr>
<td>Presence of 2 Ab</td>
<td>22 (61.1)</td>
<td>17 (47.2)</td>
</tr>
<tr>
<td>Presence of 3 Ab</td>
<td>5 (13.9)</td>
<td>6 (16.7)</td>
</tr>
<tr>
<td>Hydrops fetalis</td>
<td>6 (16.7)</td>
<td>4 (11.1)</td>
</tr>
</tbody>
</table>

### Table 2 Ante Natal Management

<table>
<thead>
<tr>
<th>Group 1, $n = 36$</th>
<th>Group 2, $n = 36$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number IUT/pregnancy</td>
<td>2.5 (1.0–5.0)</td>
<td>2.0 (1.0–6.0)</td>
</tr>
<tr>
<td>Gestational age at first IUT, wk</td>
<td>26.4 ± 3.5</td>
<td>27.6 ± 4.1</td>
</tr>
<tr>
<td>Hb at first IUT, g/dL</td>
<td>5.6 ± 2.4</td>
<td>6.7 ± 2.5</td>
</tr>
</tbody>
</table>

### Table 3 Neonatal Data

<table>
<thead>
<tr>
<th>Group 1, $n = 36$</th>
<th>Group 2, $n = 36$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age at birth, wk</td>
<td>34.1 (27.6–37.0)</td>
<td>34.9 (28.6–37.9)</td>
</tr>
<tr>
<td>Vaginal birth</td>
<td>6 (17.7)</td>
<td>18 (44.4)</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>2107.6 ± 437.0</td>
<td>2455.0 ± 507.0</td>
</tr>
<tr>
<td>Apgar &lt;7 at 5 min</td>
<td>1 (3.1)</td>
<td>2 (5.6)</td>
</tr>
<tr>
<td>Hemoglobin at birth, g/dL</td>
<td>10.2 (6.0–18.6)</td>
<td>13.4 (7.7–22.5)</td>
</tr>
<tr>
<td>Transfer to ICU</td>
<td>33 (91.7)</td>
<td>22 (61.1)</td>
</tr>
<tr>
<td>No. of top-up transfusion</td>
<td>1 (1–6)</td>
<td>1 (1–10)</td>
</tr>
<tr>
<td>Postnatal ET</td>
<td>17 (47.2)</td>
<td>7 (19.4)</td>
</tr>
<tr>
<td>Bilirubin maximal, units</td>
<td>111 (28–259)</td>
<td>126 (58–353)</td>
</tr>
<tr>
<td>Intensive PT</td>
<td>28 (77.8)</td>
<td>24 (70.6)</td>
</tr>
<tr>
<td>Total duration of PT (intensive or not), d</td>
<td>4.5 (1.0–7.0)</td>
<td>5.0 (2.0–8.0)</td>
</tr>
<tr>
<td>Neonatal death</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>
and first transfusion, and a decrease in the postnatal ET with no maternal or neonatal adverse impact of DCC. The rationale for the benefits of DCC in infants with red blood cell alloimmunization is to allow a higher rate of Hb at birth, decreasing the numbers of postnatal exchange and top-up transfusions. Previous studies in preterm and term neonates showed an increase of Hb and of hematocrit in case of DCC. In our population, we observed an increase of Hb at birth in the DDC group. We can relate this higher Hb rate to the implementation of DDC and not to a change in our practice: delay between last IUT and birth was similar between the groups and we showed in a previous study that the use of PSV MCA did not modify our antenatal management.

Our series found a significant decrease of ET in children with immune hemolytic disease after DCC. This procedure is attempted in severe anemia and/or severe hyperbilirubinemia, particularly if the PT fails. Postnatal ET rate usually varies from 16% to 71% in case of alloimmunization. This result is particularly interesting because of neonatal morbidity linked to this procedure. The mortality rate is estimated to be between 0.5% and 2.0% and the morbidity rate varies from 5.0% to 74.0%. The main complications are mainly linked to the umbilical vein cathereterization and to the transfusion risks. On the contrary, the rate of transfusions and the median number of transfusions were similar between the 2 groups. One major benefit of DCC is the delay between birth and first transfusion. We observed in our population a gain of 4 days of life before first transfusion in the DCC group. This avoids transfusion in emergencies and allows a better organization of neonatal care.

Reserves concerning DCC in red blood cell alloimmunization were the risks of overloading the newborn with additional incompatible red blood cells, leading to increased levels of bilirubin and, in very severe cases, severe jaundice and kernicterus. In our study we did not find a difference in maximal bilirubin levels in the 2 groups. In red blood cell alloimmunization, all newborns are subjected to PT in the first hours of life as well as enhanced surveillance to prevent the progression into a severe jaundice. We observed a high rate and of PT in the DCC group but a lower rate of intensive PT. There was no severe complication, such as kernicterus. This high rate of PT can be also explained by a change in our neonatal practice with systematic PT during the first hours of life in case of red blood cell alloimmunization. Data on late-onset jaundice and DCC are variable in the literature. Van Rheenen et al found an increased risk of hyperbilirubinemia of 12%, with no increase in the PT or ET needs. On the contrary, Arca et al and McDonald et al found a significant increase in neonates requiring PT after delayed clamping.

Although many randomized controlled trials have evaluated the benefits of DCC versus ICC in term and preterm infants, the ideal timing for cord clamping has yet to be established. The definition of delayed umbilical cord clamping varied between studies from 30 and 180 seconds. McDonnel et al had a mean DCC of 31 seconds. Kugelman et al and Mercer et al proposed a DCC of 30 to 45 seconds, whereas Aladangady et al had 60 to 90 seconds. The longest was 180 seconds. Our protocol was a preliminary study and we chose the minimal duration recommended (30 seconds). This study is the first to evaluate the impact of DCC in neonatal management in red cell alloimmunization. Due to the study design (before/after study), potentially covariables may be unevenly distributed between groups. One potential bias is the change in neonatal practices for PT during the study period. In the ICC group, neonates were smaller, born earlier, and more likely by cesarean. These factors may influence the study findings. However, it seems difficult to conduct a randomized trial due to the low prevalence of alloimmunization and to the known benefits of DCC.

CONCLUSIONS

DCC has already demonstrated its benefits in preterm birth, with a decrease in the transfusion needs. This study highlights a significant benefit of DCC in moderate to severe anemia secondary to red blood cell alloimmunization with resulting decreased postnatal ET needs, and an improvement in the Hb level at birth, with no severe hyperbilirubinemia. We recommend DCC with duration of 30 seconds in infants at risk for red blood cell alloimmunization neonatal anemia only if the monitoring and management of jaundice can be optimal. It will be interesting to evaluate the long-term effects of DCC in this population.

ABBREVIATIONS

DCC: delayed cord clamping
ET: postnatal exchange transfusion
Hb: hemoglobin
ICC: immediate cord clamping
IUT: in utero transfusion
MCA PSV: middle cerebral artery peak systolic velocity
PT: phototherapy

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*Pediatrics* 2016;137;
DOI: 10.1542/peds.2015-3236 originally published online February 18, 2016;

The online version of this article, along with updated information and services, is located on the World Wide Web at:

http://pediatrics.aappublications.org/content/137/3/e20153236

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