Editorial

Delayed cord clamping in red blood cell alloimmunization: safe, effective, and free?

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Abstract: Hemolytic disease of the newborn (HDN), an alloimmune disorder due to maternal and fetal blood type incompatibility, is associated with fetal and neonatal complications related to red blood cell (RBC) hemolysis. After delivery, without placental clearance, neonatal hyperbilirubinemia may develop from ongoing maternal antibody-mediated RBC hemolysis. In cases refractory to intensive phototherapy treatment, exchange transfusions (ET) may be performed to prevent central nervous system damage by reducing circulating bilirubin levels and to replace antibody-coated red blood cells with antigen-negative RBCs. The risks and costs of treating HDN are significant, but appear to be decreased by delayed umbilical cord clamping at birth, a strategy that promotes placental transfusion to the newborn. Compared to immediate cord clamping (ICC), safe and beneficial short-term outcomes have been demonstrated in preterm and term neonates receiving delayed cord clamping (DCC), a practice that may potentially be effective in cases RBC alloimmunization.

Keywords: Red blood cell (RBC); delayed cord clamping (DCC); exchange transfusions (ET)

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Hemolytic disease of the newborn (HDN) is an alloimmune disorder caused by transplacentally transmitted maternal immunoglobulin (Ig) G antibodies that bind to paternally inherited antigens present on fetal red blood cells (RBCs) resulting in hemolysis, which leads to elevated bilirubin levels (1). After delivery, without placental clearance, hyperbilirubinemia may develop from ongoing RBC hemolysis, which places neonates at increased risk for central nervous system damage. Moderate hyperbilirubinemia may result in symptoms of bilirubin-induced neurologic dysfunction, a disorder associated with long-term developmental delay, cognitive problems, executive function impairment, and behavioral and psychiatric disorders (2). More severe hyperbilirubinemia has been associated with the development of kernicterus, an irreversible condition characterized by choreoathetoid cerebral palsy, impaired upward gaze, and sensorineural hearing loss (2).

In cases refractory to intensive phototherapy treatment, exchange transfusions (ET) may be performed to prevent kernicterus by reducing circulating bilirubin levels and to replace antibody-coated RBCs with antigen-negative RBCs. In sick neonates, ETs have been associated with adverse events (e.g., hypocalcemia and thrombocytopenia) and more severe complications, such as death (3,4). More recent literature suggests that ET rates have decreased compared with historical data (5,6). Although mortality and morbidity is reported in association with ET, the true ET-associated risks are challenging to determine since ETs are often performed in premature neonates whose have pre-existing increased risks of mortality and morbidity (5). Since ETs require vascular access, additional resources (e.g., sterile equipment, one to two medical officers, nursing staff, a blood warmer, and cytomegalovirus-negative blood), and are associated with increased risks to neonates, safe, effective strategies to avoid ETs are desired.

Delayed cord clamping (DCC) may be a safe, effective, cost-free strategy to prevent the need for ET in cases of

RBC alloimmunization. A recent single center, retrospective cohort study by Garabedian *et al*. entitled "Benefits of delayed cord clamping in red blood cell alloimmunization," sheds light on another possible short-term advantage of DCC (7). To assess the risk and benefits of DCC in cases of RBC alloimmunization the authors performed a comparative before and after study of 72 neonates who had received in utero transfusions (IUTs) for fetal anemia. They compared two groups of neonates: one group (n=36) who had immediate cord clamping (ICC) during the first study period (January 2001–June 2009) and one group (n=36) who had DCC for 30 seconds after birth during the second study period (June 2009–December 2014). Compared to the neonates who had ICC, the neonates who received DCC were less anemic (7 of 36 *vs*. 24 of 36 neonates, P=0.004), had higher hemoglobin levels measured within 1 hour after birth (13.4 *vs*. 10.2 g/dL, P=0.0003), and required less ET postnatally (19.4% *vs*. 47.2%, P=0.0124). There were no significant differences in maximum bilirubin levels and intensive phototherapy rates or total phototherapy treatment duration between the two groups. Unexpectedly, the number of postnatal top-up transfusions was similar between the ICC and DCC groups, which could possibly be explained by dissimilar antibody levels, however, antibody levels were not reported. None of the neonates in the study died.

In the study by Garabedian *et al*., the postnatal differences in anemia, hemoglobin levels measured within 1 hour after birth, and the numbers of ETs did not appear to be secondary to antenatal discrepancies between the groups from the two study periods. There was not a significant difference between the two groups regarding the number of IUTs, hemoglobin levels at first IUT, the delay between last IUT and delivery, and middle cerebral artery peak systolic velocity greater than 1.5 multiples of the median (signifying fetal anemia). However, there were group differences apparent at birth. The median gestation age at birth was slightly higher in the DCC group compared to the ICC groups, 34.9 (range, 28.6–37.9) *vs*. 34.1 (range, 27.6–37.0) weeks, respectively, (P=0.0350). More infants in the DCC group were born vaginally (44.4%; 16/36) than in the ICC group (17.7%; 6/36), (P=0.0158), and neonates from the DCC group had a higher birth weight (2,455±507 grams) than neonates from the ICC group (2,107.6±437 grams), (P=0.0029). Whether or not the abovementioned group differences influenced outcomes such as hemoglobin levels or the need for ETs is not clear.

In newborns, DCC appears safe (8,9), efficacious, and is free, which is a rarity in modern-day medicine. At birth, unlike ICC, DCC allows time for placental transfusion to the newborn. In preterm neonates, DCC for at least 30 seconds has been associated with improved hematocrit levels, mean systemic blood pressure, urine output, and cardiac function after birth (10). DCC is also associated with a decrease in intraventricular hemorrhage (all grades), need for vasopressors, number of blood transfusions during the neonatal period in premature neonates, necrotizing enterocolitis, and overall mortality (10,11). In term neonates, DCC is associated with decreased iron deficiency up to 6 months of age (9,12) and improved fine-motor and social domain scores at 4 years of age, especially in boys compared to ICC (13).

In line with the growing evidence supporting DCC, multiple authoritative governing bodies have endorsed DCC, including The World Health Organization (14), the American Academy of Pediatrics (15), and the European Association of Perinatal Medicine (16). Since 2012, the American College of Obstetricians and Gynecologists Committee Opinion, has advocated DCC in preterm infants, when feasible (15), yet many obstetricians have not adopted this practice. The 2015 Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care of the Neonate issued by the American Heart Association and American Academy of Pediatrics, which serve as the foundation for the upcoming Neonatal Resuscitation Program® 7th edition materials (https://eccguidelines.heart.org/index.php/circulation/cpr-ecc-guidelines-2/part-13-neonatal-resuscitation/, accessed 27 March 2016), advocate that cord clamping should be delayed for at least 30 to 60 seconds for most vigorous term and preterm newborns. Despite endorsement by these governing bodies and the multiple randomized control trials demonstrating the safety and short-term benefits of DCC (8-11,17), implementation of this placental transfusion practice still has not been universal (18).

The study by Garabedian *et al*. adds to list of potential benefits of DCC. In neonates with HDN, DCC may be viewed as a safer strategy than ICC since it prevented the need for ET and the overall exposure to risk-associated interventions was decreased with DCC (7). In addition, more neonates in the ICC group (91.7%, 33/36) required transfer to the ICU compared to the DCC group (61.1%, 22/26) (P=0.0023), which likely affected overall hospitalization costs. The study by Garabedian *et al*. supports DCC as a potentially feasible strategy to prevent ET without more neonatal complications due

to hyperbilirubinemia. The main antibody detected in their study cohort was Rhesus D (RhD), present in 80.6% in ICC group and 72.2% in the DCC group. Although severe cases of HDN alloimmunization against the RhD antigen have significantly decreased since introduction of anti-D immunoglobulin (Ig) prophylaxis, 1 to 3 per 1,000 D-negative women still develop anti-D despite antenatal and postnatal anti-D Ig prophylaxis (19). In low to middle income countries, where Rh disease remains a major cause of hyperbilirubinemia and kernicterus (20), DCC may be a beneficial strategy to reduce complications related to HDN. Globally, information on RBC alloimmunization is limited, especially in low to middle income regions like Southern Asia and Sub-Saharan Africa, where over 2 billion people live. A recent meta-analysis estimated that RBC alloimmunization among transfused patients in Sub-Saharan Africa is quantitatively similar to high income countries, where antibody screening is common, but is qualitatively different, with anti-E the most common clinically significant antibody, followed by anti-K, anti-C and anti-D (21). In these resource poor settings, where the screening and treatment of RBC alloimmunization remains a tremendous medical and economic challenge, safe, inexpensive, and practical pre- and postnatal approaches are needed to decrease morbidity and mortality (20).

While safety and efficacy are essential for optimal neonatal care practices, financial costs should also be considered when assessing therapeutic approaches. Treatment interventions to prevent serious hyperbilirubinemia related to RBC alloimmunization, such as ET and intravenous immunoglobulin (IVIg) administration are not risk-free, and increase hospitalization costs. IVIg, a donor-derived blood product, may be associated with rare complications including transfusion reactions, renal failure, hemolysis, and necrotizing enterocolitis (22,23). The efficacy of IVIg for neonates with HDN due to RhD and ABO isoimmunization remains unclear based on a recent systematic review that included ten trials of Rh isoimmunization (n=463) and five trials of ABO isoimmunization (n=350) (24). Given the financial costs, the risks of ET, and the questionable efficacy of IVIg, therapeutic strategies such as DCC seem sensible, but require further study to better establish evidence-based practice.

Accurate non-invasive prenatal diagnosis methods using fetal DNA extracted from maternal plasma can now be performed in the first trimester of pregnancy to screen for RhD-negative pregnant women with RhD-positive circulating fetal DNA using circulating cell-free fetal DNA molecular techniques (1). This approach reduces the need for invasive procedures for detecting putative antigens, most notably RhD, in fetuses of alloimmunized pregnancies and allows for targeted antenatal anti-D prophylaxis for RhD-negative pregnant women. The use of non-invasive prenatal diagnosis methods coupled with DCC at birth may further improve management of fetuses with HDN and decrease the risk for postnatal morbidity.

Research continues to accumulate supporting the feasibility, safety, efficacy, and benefits of DCC (7-11,13,17) and umbilical cord milking (12,25). Regarding cases of RBC alloimmunization, future studies need to determine the optimal duration of DCC and also whether umbilical cord milking is a safe and efficacious therapeutic option. Further studies are also needed to clarify if DCC is efficacious for all types of maternal RBC alloantibodies and also to determine long-term outcomes beyond hospital discharge.

Since newborns with HDN may present with anemia and hydrops, studies are needed to clarify whether or not an additional blood volume at birth from DCC is beneficial in these patients. Enrolling fetuses with hydrops in a research trial may not be feasible and therefore the answer to this question may be limited to case series or case control studies. When considering the risks and benefits of strategies aimed at optimizing neonatal outcomes, the study by Garabedian adds further emphasis that patience should be practiced at birth before clamping the cord and that immediate clamping has a potential cost. While more long-term follow-up data is needed, the short-term benefits of DCC appear encouraging, especially when considering DCC takes less than a minute.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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