Delayed Versus Immediate Cord Clamping in Preterm Infants

William Tarnow-Mordi, Jonathan Morris, Adrienne Kirby, Kristy Robledo, Lisa Askie, Rebecca Brown, Nicholas Evans, Sarah Finlayson, Michael Fogarty, Val Gebski, Alpana Ghadge, Wendy Hague, David Isaacs, Michelle Jeffery, Anthony Keech, Martin Kluckow, Himanshu Popat, Lucille Sebastian, Kjersti Aagaard, Michael Belfort, Mohan Pammi, Mohamed Abdel-Latif, Graham Reynolds, Shabina Ariff, Lumaan Sheikh, Yan Chen, Paul Colditz, Helen Liley, Margo Pritchard, Daniele de Luca, Koert de Waal, Peta Forder, Lelia Duley, Walid El-Naggar, Andrew Gill, John Newnham, Karen Simmer, Katie Groom, Philip Weston, Joanna Gullam, Harshad Patel, Guan Koh, Kei Lui, Neil Marlow, Scott Morris, Arvind Sehgal, Euan Wallace, Roger Soll, Leslie Young, David Sweet, Susan Walker, Andrew Watkins, Ian Wright, David Osborn, and John Simes, for the Australian Placental Transfusion Study Collaborative Group

National Health and Medical Research Council Clinical Trials Centre, University of Sydney (W.T.-M., A. Kirby, K.R., L.A., R.B., S.F., V.G., A. Ghadge, W.H., A. Keech, L. Sebastian, J.S.); University of Sydney (J.M., N.E., M.F., D.I., M.J., M.K., H. Popat, H.L., D.O.); Royal North Shore Hospital (Y.C.); University of New South Wales (K.L.), Sydney; Australian National University, Canberra (M.A.-L., G.R.); University of Queensland, Brisbane (P.C., H.L., M. Pritchard); James Cook University, Cairns (G.K.); University of Western Australia, Perth (A. Gill, J.N., K.S.); Flinders University, Adelaide (S.M.); Monash University (A.S., E. W.); University of Melbourne (S.W.), Melbourne; Mercy Hospital for Women, Heidelberg (A.W.); University of Newcastle, Newcastle (K.W., P.F.); University of Wollongong, Wollongong (I.W.), Australia; Baylor College of Medicine, Houston, TX (K.A., M.B., M. Pammi); Aga Khan University Hospital, Karachi, Pakistan (S.A., L. Sheikh); Hôpital Antoine-Beclere, Clamart, France (D.L.); University of Nottingham, Nottingham, United Kingdom (L.D.); Dalhousie University, Halifax, Nova Scotia, Canada (W.E.-N.); University of Auckland, Auckland (K.G.); University of Otago, Dunedin (P.W., J.G., H. Patel), New Zealand; University College London, London (N.M.); Royal Jubilee Maternity Hospital, Belfast (D.S.), United Kingdom; and University of Vermont, Burlington, VT (R.S., L.Y.)

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ABSTRACT

Systemic reviews have shown that delaying the time of umbilical cord clamping can improve outcomes of preterm newborns. One such study found enhanced placental transfusion through delayed cord clamping, cord-palpation, or a combination of the 2 practices caused a lower infection and mortality rate when compared with immediate clamping. Despite this recent body of evidence, concerns exist about harm from delayed resuscitation and hyperbilirubinemia causing current professional guidelines to vary significantly.

This unblinded, randomized controlled trial compared the rates of a composite outcome of death and major morbidity between delayed and immediate cord clamping in infants born before 30 weeks of gestation. This study took place in 25 participating centers across 25 countries between 2010 and 2017. Eligible participants were randomly assigned to receive either immediate cord clamping defined as clamping within 10 seconds after delivery or delayed clamping defined as clamping at 60 or more seconds without cord palpation. The primary study outcomes were death, severe brain injury, severe retinopathy of prematurity, necrotizing enterocolitis, and late-onset sepsis, each diagnosed by 36 weeks of postmenstrual age. Tests for interaction were used to detect heterogeneity in the data between the primary outcomes across 3 subgroups: gestational age (<27 weeks vs ≥27 week), sex, and method of delivery.

A total of 1566 infants were deemed eligible for the study with 782 assigned to immediate cord clamping and 784 assigned to delayed cord clamping. The average times of clamping for the delayed and immediate cohorts were 60 seconds and 5 seconds, respectively. Adherence to the randomized protocol varied between the groups (94.9% for the immediate cohort, 73.2% in the delayed cohort) with the primary reason for nonadherence in the delayed cohort being clinical concern about infant well-being. No significant difference was found in the primary outcome at 36 weeks between immediate clamping (37.2%) and delayed clamping (37.0%) (relative risk [RR], 1.00; 95% confidence interval [CI], 0.88–1.13; $P = 0.96$). Death by 36 weeks postmenstrual age occurred in 9.0% of those in the immediate cohort and 6.4% in the delayed clamping group (RR, 0.69; 95% CI, 0.49–0.97; $P = 0.03$ unadjusted and 0.39 after post hoc adjustment for multiple secondary comparisons). More infants in the immediate clamping cohort received red blood cell tranfusions

(60.5% vs 52.1% in the delayed clamping cohort). There were no significant differences in Apgar score, peak bilirubin level, or other major morbidities.

The results of this study show that there is no significant difference on the rates of mortality or major morbidity at 36 weeks of gestation among preterm infants receiving immediate umbilical cord clamping versus delayed clamping.

EDITORIAL COMMENT

(Over the past decade plus, evidence has accumulated that delayed cord clamping at time of delivery, an item previously only seen in more "natural" deliveries, may have benefit in both preterm and term neonates. In the Cochrane review of preterm neonates from 2012, there were 15 studies included (738 infants) and delayed cord clamping was associated with fewer infants requiring transfusions for anemia (7 trials, 392 infants; RR, 0.61; 95% CI, 0.46–0.81), less intraventricular hemorrhage (RR, 0.59; 95% CI, 0.41–0.85), and lower risk for necrotizing enterocolitis (RR, 0.62; 95% CI, 0.43–0.90) compared with immediate clamping. However, the peak bilirubin concentration was higher for infants allocated to delayed cord clamping compared with immediate clamping (7 trials; 320 infants; mean difference, 15.01 mmol/L; 95% CI, 5.62–24.40). For most other outcomes (including the primary outcomes infant death, severe [grade 3–4] intraventricular hemorrhage, and periventricular leukomalacia), there were no clear differences identified between groups; but for many there was incomplete reporting and wide CIs. Outcome after discharge from hospital was reported for one small study; there were no significant differences between the groups in mean Bayley II scores at age 7 months (corrected for gestation at birth [58 children]). No studies reported outcomes for the women.

For term neonates, it seems that the potential benefit is smaller. In one meta-analysis, the benefits associated with late cord clamping included improved hematologic status measured as hematocrit, iron status as measured by ferritin concentration, and stored iron, as well as a reduction in the risk of anemia (RR, 0.53; 95% CI, 0.40–0.70) (*JAMA* 2007;297:1241–1252). However, neonates with delayed clamping were at increased risk of experiencing asymptomatic polycythemia (RR, 3.82; 95% CI, 1.11–13.21). There is no evidence to suggest an impact on neonatal mortality or severe neonatal morbidity in term neonates.

So there remains a need for larger studies with long-term outcomes in both term and preterm neonates. In the current study, abstracted previously, the authors conducted a large, prospective, multicenter, randomized trial to examine delayed cord clamping in preterm neonates on severe morbidity and mortality outcomes. They randomized more than 1500 preterm neonates to delayed versus early cord clamping and followed the neonates through their hospital course and beyond. There was no difference in the primary outcome (death or major neonatal morbidity) at 37.2% versus 37.0% (immediate vs delayed). However, when death was examined alone, there was a reduction in death in the delayed cord clamping group from 9.0% in the immediate group versus 6.4% in the delayed cord clamping group. However, this difference when accounting for multiple comparisons was not statistically significant.

Although this study was a large, randomized trial, because of the existing research, the findings of the trial are less impactful. The study was conducted from 2009 to 2017, and during that time, the literature on the potential benefit in preterm neonates became more solidified and the practice more widely adopted. Further, although this study was fundamentally negative, the most important outcome of interest was neonatal mortality, which was numerically (if not statistically) improved. Given that existing systematic reviews and meta-analyses have demonstrated a positive impact on preterm neonates, as these data are incorporated into these reviews, it is likely that they will continue to be positive. Thus, I believe the standard practice will continue to be delayed cord clamping in preterm neonates. Term neonates may also receive benefit, albeit smaller, and require additional study.—ABC)