Randomized Study of Delayed Cord Clamping of 30 to 60 Seconds in the Larger Infant Born Preterm

Laura J. Perretta, MD, Morgan Spaight, MD, Vivien Yap, MD, and Jeffrey Perlman, MB, ChB

In a randomized study of infants born preterm (gestational age 28-34 6/7 weeks), we evaluated delayed cord clamping for 30 (n = 50) vs 60 (n = 55) seconds. The primary outcome of initial hematocrit differed by 2.8% (P = .006), being greater with 60 seconds. There were no differences in secondary outcomes and no adverse consequences between groups. These findings should serve as a stimulus to many centers that are reluctant to implement delayed cord clamping in this targeted larger premature population. *(J Pediatr 2020;224:153-7).*

Delayed cord clamping (DCC) increases the volume of blood transferred from placenta to infant at the time of delivery and facilitates cardiorespiratory transition at birth.[1-4] Systematic reviews of randomized studies comparing early vs DCC of varying duration show advantages to DCC.[5,6] The most recent systematic Cochrane review included 25 studies involving 3100 newborns who were born premature delivered between 24 and 36 weeks of gestation with DCC times ranging between 30 and 180 seconds, with most studies delaying for 30-60 seconds, and found that DCC, when compared with early cord clamping of <30 seconds, was associated with a probable reduction in neonatal mortality but no difference in severe intraventricular hemorrhage or chronic lung disease.[1]

Several professional organizations have published guidelines supporting the practice of DCC in infants born preterm. The American College of Obstetricians and Gynecologists committee opinion now recommends a delay in umbilical cord clamping in vigorous infants born term and preterm for at least 30-60 seconds after birth.[7] The World Health Organization recommends that the umbilical cord not be clamped earlier than 1 minute after birth in babies who do not require positive pressure ventilation (PPV),[8] and the American Heart Association guidelines concur that DCC for longer than 30 seconds is reasonable for both infants born term and preterm who do not require resuscitation.[9]

Nevertheless, delayed clamping is not universally performed, owing to continuing anxiety about the risks of delayed resuscitation or hyperbilirubinemia.[1] Furthermore, the practice of DCC may vary between institutions due to the lack of a specific guideline or protocols for DCC in this targeted population.[10,11] Before we implemented this study, there was a range of practice in our institution, with some providers preferring to immediately clamp the cord, and others delaying cord clamping from 30 to up to 90 seconds in newborns born at term, with much more uncertainty in the preterm population.

The primary objective of this study was to determine, in a population of infants born preterm of 28-34$^{6/7}$ weeks gestational age not requiring resuscitation, whether DCC for 30 vs 60 seconds would be associated with difference in hematocrit of 3%. A secondary objective was to determine the effect of DCC on additional measures such as Apgar scores, initial and 6-hour heart rate (HR), initial temperature, initial and 6-hour blood pressure, fluid resuscitation and/or the need for pressors, peak bilirubin, and days on phototherapy.

Methods

This was a randomized trial conducted in the delivery room and neonatal intensive care unit (NICU) at New York Presbyterian Hospital Weill Cornell Medicine from July 2015 through June 2018. Mothers with threatened preterm delivery between 28 and 34$^{6/7}$ weeks of estimated gestational age were approached for written informed consent before delivery. Exclusion criteria included any suspicion of placental disruption, such as suspected placental abruption or placenta previa, mono-di twin gestation, reversal or absence of flow on Doppler ultrasound of umbilical arteries, terminal bradycardia, cord prolapse, or antenatally identified major congenital anomalies.

Following consent, infants were assigned randomly to receive either 30 or 60 seconds of DCC. This occurred immediately before delivery using sealed envelopes with a predetermined randomization using a random number generator. The designated study arm was revealed to the delivery room staff including the obstetrician, neonatal fellow, neonatal resuscitation nurse, and labor and delivery nurses (**Figure 1**). In all cesarean deliveries, the NICU fellow was in a sterile gown and gloves to assess the infant on a sterile

BW	Birth weight
CPAP	Continuous positive airway pressure
DCC	Delayed cord clamping
HR	Heart rate
LOS	Length of stay
NICU	Neonatal intensive care unit
PPV	Positive pressure ventilation

From the Division of Newborn Medicine, Department of Pediatrics, New York Presbyterian-Weill Cornell Medicine, New York, NY

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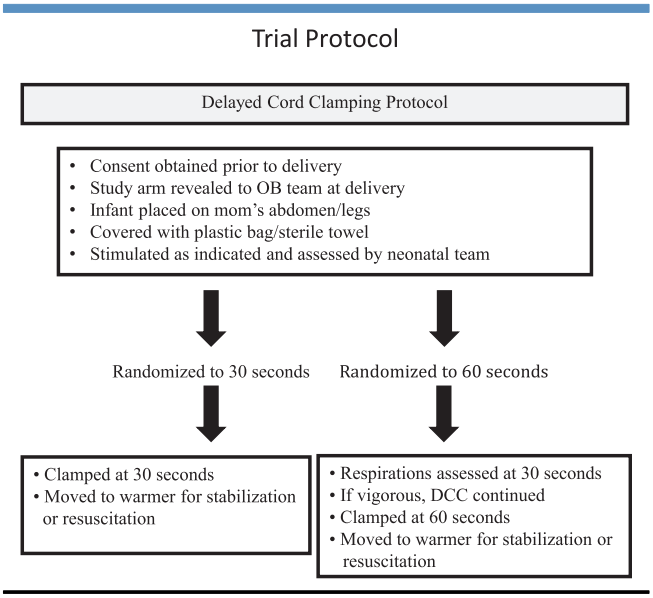

Figure 1. Trial protocol with contraindications. *OB*, obstetrics.

field. Infants of multiple births underwent randomization as a pair. A timer was started immediately upon delivery, with one person designated to record the onset of initial respirations and umbilical cord clamping. With a vaginal delivery, the infant was placed between the mother's legs, and in the instance of a cesarean delivery on the mother's abdomen in all cases. The neonatal fellow assisted with the initial steps of stabilization including drying, stimulating, clearing of the mouth of secretions, and covering the infant in a polyethylene bag as indicated. The team assessed the infant for onset of respirations. If the infant was apneic at 30 seconds, the cord was clamped and the infant was transferred to the warmer for appropriate resuscitation regardless of the assigned study arm. If the infant demonstrated respiratory effort, the cord remained unclamped to the full assigned study arm of 60 seconds, if applicable. The permissible target range variation was 3 seconds for the 30-second group and 5 seconds for the 60-second group.

Following cord clamping, the infant underwent stabilization and/or resuscitation as indicated, which included any respiratory support, ie, PPV, continuous positive airway pressure (CPAP), and/or intubation. Infants were then transferred to the NICU, where they received standard neonatal care. The treating attending neonatologist was blinded to the assignment of cord clamping. The infant's medical records were assessed for the following: birth weight (BW), estimated gestational age, twin set or singleton, mode of delivery, Apgar score at 1 and 5 minutes, time to onset of respirations, actual cord clamping time, resuscitation interventions in the delivery room, temperature in the delivery room before transfer, initial temperature on admission to the NICU, initial hematocrit, initial glucose, admitting heart and blood pressure and repeated at 6 hours, need for a fluid bolus or inotrope use for a low blood pressure, peak bilirubin level, duration of phototherapy, and need for a partial exchange transfusion. Additional data retrieved included urine output in mL/kg/h in the first 24 hours, requirement for ventilation at 24 hours, and duration of hospitalization.

Approval was obtained through the Weill Cornell Medical College institutional review board. A data safety–monitoring committee was assigned, which reviewed the data every 6 months, and the study was registered with the clinical trials database. (NCT02478684).

Statistical Analyses

The study was designed to test the hypothesis that prolongation of DCC from 30 to 60 seconds in this preterm population would result in an increase of 3 percentage points in hematocrit. To detect this difference with 80% power using a 2-sample *t* test with .05 2-sided significance level, it was projected that the study would require 150 enrolled infants or approximately 75 in each arm (30- and 60-second DCC). The infants were analyzed by intention to treat in the designated study arms regardless of the actual duration of DCC. Descriptive statistics (mean, median, SD, percent, etc) were used to describe the patient population. χ^2, paired, or standard *t* tests were used as appropriate. A multivariate regression analysis was employed to include variables that may have influenced length of stay (LOS), including gestational age, BW, onset of respirations, admitting temperature, initial HR, initial blood pressure, and initial hematocrit. All analyses were performed in SAS, version 9.3 (SAS Institute, Inc, Cary, North Carolina).

Results

In total, 374 infants born preterm were eligible for enrollment; of these, 269 were not enrolled due to declined consent (approximately one-third) or as a result of missed opportunities (Figure 2). This resulted in 105 infants randomized, with 50 infants allocated to the 30-second and 55 infants to the 60-second DCC group. This difference reflected 8 and 12 twin sets consented in the 30- and 60-second groups, respectively. The study was terminated early due to fall off in recruitment. This was as a result of maternal desire for at least 60 seconds of DCC over time, as well as loss of equipoise of the obstetricians also preferring a longer delay in cord clamping.

The actual measured clamp times were 32.4 ± 11 seconds (median 30, IQR 28, 60) and 58.5 ± 15 seconds (median 59.1, IQR 10, 100) for the 30- and 60-second groups, respectively. The rate of adherence to randomized treatment was 92% in the 30-second and 94% in the 60-second treatment group.

The groups were similar in terms of BW, gestational age, and delivery via cesarean (Table). The onset of respirations occurred at a mean of 11 ± 12 seconds vs 13 ± 15 seconds in the 30- and 60-second groups, respectively (P = .24). Following cord clamping, 42% of both groups received either CPAP or PPV, and 6 infants (12%) in the 30-second

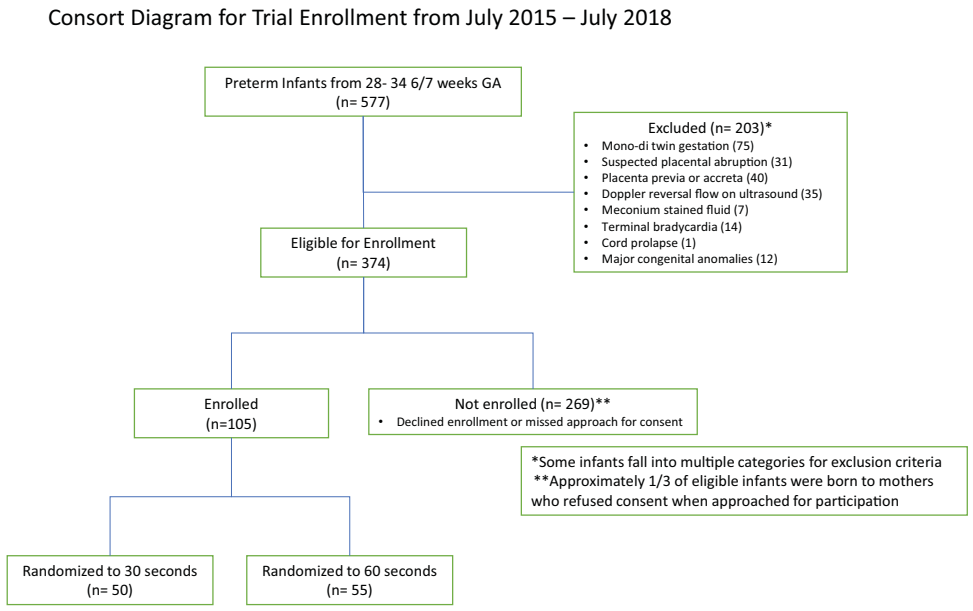

Figure 2. CONSORT diagram for trial enrollment from July 2015 to July 2108.

group and 9 (16%) infants in the 60-second group were intubated in the delivery room (Table).

There was a significant difference in initial hematocrit in the NICU, ie, 49.7 ± 5.2 vs 52.5 ± 6.1 in the 30- vs 60-second groups, respectively (P = .006) (Table). Posthoc subgrouping analysis by gestational age revealed that for infants <31 weeks, the hematocrit increased from 45.9 ± 6.2 to 52.7 ± 7.6 in the 30- vs 60-second group (P = .03), and for infants >31 weeks, the hematocrit increased from 50.1 ± 4.8 to 52.5 ± 5.9 in the 30- vs 60-second group (P = .02) (Table).

There were no differences in HR or mean blood pressure at admission and at 6 hours of life between the 2 groups. When we compared initial and 6-hour HR by individual infants (paired t test), there was a 24 ± 13 beats/min decrease for the 30-second group (P = .0005) and a 21 ± 16 beats/min decease for the 60-second group (P = .00005). When we compared initial and 6-hour blood pressure, there were no differences for the 30-second (–1.5 ± 5 mm Hg, P = .16) and 60-second groups (0.01 ± 2, P = .50) respectively (paired t test). There was no difference in the need for volume and/or pressor support (2% in both groups), initial admission temperature, the number of infants with an initial temperature <36°C, peak bilirubin levels, or the number of days on phototherapy. No infant presented with polycythemia or required a partial exchange transfusion.

At 24 hours, there was no difference in the use of noninvasive respiratory support (high-flow nasal cannula and/or CPAP 23/25 [46%] vs 20/55 [36%] [P = .32] or intubation (1/50 [2%] vs 2/55 [4%] for the 30- vs 60-second groups, respectively). Three infants in the 30-second group received surfactant vs none in the 60-second group. The initial 24-hour urine output was greater for the 60- vs 30-second groups (3.2 ± 0.08 vs 3.0 ± 0.9 mL/kg/min, P = .049). No infants in the study died.

The LOS for the infant's hospital course was shorter in the 60- vs 30-second group (19 days [IQR 12 to 32] vs 29 days [IQR 13 to 35], respectively, P = .01). In post-hoc multivariate analysis, there was no difference between the groups for LOS after adjusting for gestational age and BW.

Discussion

The principal finding of this randomized study of DCC was a 2.8% difference in hematocrit, favoring the longer delay in cord clamping of 60 seconds. Heart rate fell over the first 6 hours in both groups, with no differences in mean blood pressure noted. The majority of infants established spontaneous respirations within 30 seconds, with a mean onset of ≤15 seconds in both groups, which is consistent with a previous report.[12]

DCC increases the volume of blood transferred from placenta to infant at the time of delivery.[1] The finding of a 2.8% difference between groups is consistent with this concept and akin to a recent meta-analysis that showed a similar increase when comparing early with DCC.[6] We also found a 7% greater increase in hematocrit in the infants with gestational age <31 weeks, similar to a report by Song et al showing 7% greater hematocrits with DCC of 65-75 seconds relative to 30-45 seconds in infants <28 weeks.[13]

DCC had no effect on need for respiratory support, with 42% of infants requiring CPAP in the delivery room, with similar rates noted at 24 hours. The initial respiratory distress may reflect the high cesarean delivery rate (64 percent) in both groups, with the potential for retention of lung fluid. Whether the added volume from the placental transfusion contributed to this initial respiratory distress is unknown.

Table. General characteristics, delivery room resuscitation, postnatal transition, and potential adverse events

Characteristics	30-s Target (n = 50)	60-s Target (n = 55)	Significance
BW, g	1930 ± 431	1982 ± 461	.54
Gestational age, wk	32.7 ± 1.6	33.2 ± 2.1	.28
Mode of delivery (NSVD)	18/50 (36%)	20/55 (36%)	1
Onset to breathing, s	11 ± 12	13 ± 15	.24
Actual clamp time, s	33.2 ± 11	58.5 ± 15	.00005
Delivery room resuscitation			
Apgar <7 at 1 min	6/50 (12%)	6/55 (11%)	1
CPAP/PPV in DR	21/50 (42%)	23/55 (42%)	1
Intubation in DR	6/50 (12%)	9/55 (16%)	.58
Primary outcome			
Hematocrit, %	49.7 ± 5.2	52.5 ± 6.1	.006
Infants <31 wk gestational age (n = 16)	45.9 ± 6.2	52.7 ± 7.6	.03
Infants ≥31 wk of gestational age (n = 89)	50.1 ± 4.8	52.5 ± 5.9	.02
Postnatal transition			
Admission HR	157 ± 15	152 ± 16	.12
6-h HR	133 ± 10	132 ± 11	.63
Admission vs 6-h HR*	24 ± 13†	21 ± 16†	.00005
Admission mean blood pressure	35.7 ± 5.8	37.3 ± 6.9	.13
6-h mean blood pressure	38.9 ± 6.0	37.3 ± 5.3	.16
Admission vs 6-h blood pressure*	−1.5 ± 5#	0.01 ± 2##	#.16, ##.50
Volume ± pressors	1/50 (2%)	1/55 (2%)	1
Potential adverse events			
Admission temperature, °C	36.7 ± 0.55	36.6 ± 0.53	.29
Admission temperature <36 °C	3/50 (6%)	5/55 (9%)	.71
Peak bilirubin, md/dL	10.4 ± 2.7	10.9 ± 2.5	.18
Days on phototherapy	2.2 ± 1.6	2.4 ± 1.6	.69

DR, delivery room; *NSVD*, normal spontaneous vaginal delivery.
Difference between admission and 6 hour BP for the 30 second group. ## Difference between admission and 6 hour BP for the 60 second group.
*Paired analysis.
†Significance for both differences.

As anticipated, there was a significant decrease in HR between initial and the 6-hour measures for both groups. Although mean blood pressure did not differ between groups, urine output was greater in the 60- vs 30-second DCC group. This may reflect a positive effect of the increase in volume delivered by the longer duration of DCC.

Although not an objective of our study, we noted shorter LOS in the 60-second vs the 30-second DCC group; however, this difference did not persist after adjusting for gestational age and BW. Duley et al showed no difference in LOS when comparing immediate (≤20 seconds) vs longer DCC (≥2 minutes) in infants born premature at <32 weeks of gestational age.[14]

There were no obvious adverse effects attributable to the study. This may in part reflect the presence of a scrubbed neonatal fellow in the delivery room facilitating transition. Specifically, there was no difference in the number of infants who presented with moderate hypothermia on admission to the NICU (6% and 9% for the 30- and 60-second groups, respectively), which is comparable with that of infants subjected to immediate cord clamping and admitted to our unit.[15] No infant required a partial exchange transfusion, and the use of phototherapy was comparable between groups. Although not part of our secondary outcomes, there was no increase in postpartum hemorrhage noted during the study period (data not shown), consistent with a recent randomized study.[16]

We elected to compare 30 vs 60 seconds, as this is what the American College of Obstetricians and Gynecologists committee opinion recommended.[7] The World Health Organization recommends that the umbilical cord not be clamped earlier than 1 minute after birth in babies who do not require PPV.[8] A recent study in infants born premature at <32 weeks showed no differences in outcome when comparing immediate cord clamping (≤20 seconds) vs ≥ 2 minutes of DCC, where the baby received resuscitation beside the mother.[14] In this setup, additional people were needed at the surgical field or delivery table to monitor the infant and provide respiratory support as indicated. We conclude the optimal time to delay cord clamping remains unclear, but 60 seconds appears feasible and reasonable in spontaneously breathing premature infants.

The study has several limitations. We elected not to include a control group and only compared 30 vs 60 seconds, as suggested in the American Heart Association guidelines.[9] This reflected our consensus at the time of study initiation that immediate cord clamping could not be justified based on the prevailing evidence and different council guidelines.[8-10] In addition, the study was terminated early. This reflected increased numbers of parents declining consent (preferring a longer time of DCC), as well as loss of equipoise by the obstetricians over time, also preferring the longer duration of DCC. Strengths include a randomized study design blinded to the care providers in the intensive care unit.

In conclusion, this study adds to growing evidence for short-term clinical benefits of DCC without adverse effects in larger infants born preterm. We noted a related shift over time in attitude and acceptance among the obstetricians of a longer delay in cord clamping. These findings may serve as a stimulus to many centers who are reluctant to implement DCC in larger infants born premature. ■

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Reprint requests: Dr Jeffrey Perlman, Weill Cornell Medical College, 1300 York Ave, Suite N-506, New York, NY 10065. E-mail: jmp2007@med.cornell.edu

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