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Time to Delay: A Literature Review of Delayed Cord Clamping

Amitai Kohn*

Department of Neonatology, Beaumont Children's Hospital, Royal Oak, MI, USA

Abstract

Although the optimal time for clamping the umbilical cord has, for many years, been a source of active debate, studies in the last decades provide good evidence in support of Delayed Cord Clamping (DCC). Documented benefits of delayed cord clamping in preterm infants includes decrease in Intraventricular Hemorrhage (IVH) and Necrotizing Enterocolitis (NEC), shorter hospital stays, and improved developmental outcome. Term infants have less early anemia and better iron stores and, in limited resource countries, better nutrition and less late anemia. This review will describe historical and more recent information about the practice of delayed umbilical cord clamping, the impact on both term and preterm infants as well as the effects on the laboring mother.

Keywords: Delayed cord clamping; Immediate cord clamping; Preterm newborn; Term newborn; Post partum hemorrhage

Introduction

The timing of umbilical cord clamping during the third stage of labor has been a point of contention for many years. The estimated combined blood-volume of the fetal and placental unit is 105-110 ml/kg [1,2]. Two thirds of this volume is in the fetal circulation and one third in the placenta. In his publication "Zoonomia; or The Laws of Organic Life" originally published in 1794, Erasmus Darwin was a proponent of late or delayed umbilical cord clamping [3]. Proponents of DCC site partuition in primates and other mammalian species as an example of "nature taking its course" while some early textbooks recommend early or immediate cord clamping (ICC) to facilitate neonatal resuscitation [4-6]. In "Lotus birth" or umbilical non-severance, the umbilical cord is not clamped and, the detachment occurs naturally and may take as long as 3 days [7].

The physiology of umbilical cord occlusion is not completely understood. It is partially explained by Wharton's jelly collapse, due to smooth muscle contraction and environmental decrease in temperature. Vasoconstrictors such as 5-hydroxytryptamine, thromboxane A2, and serotonin play a role in this process as well [8-10]. In addition, an incremental increase in oxygen partial pressure (pAO_2), may promote contracting of longitudinal muscles within the umbilical cord [11]. One might speculate that the decrease in pulmonary pressure occurring with initiation of breathing, contribute to the umbilical artery constriction and promote umbilical cord occlusion as well.

Yao et al. showed that in term infants, within one minute of cord clamping, approximately 50% of the placental volume was transfused to the infant [1], and an additional 20-35 ml/kg will be transfused if the cord is not clamped for 3 minutes (Figure 1). They also showed [12] that if the infant was held 40 cm below the placenta, the transfusion was completed within 30 seconds but holding the infant either 10 cm above or 10 cm below the placenta had no effect on the volume transfused. Interestingly, a placental transfusion of the same volume still occurred when the infant was 60 cm above the placenta. This might be explained by opposing umbilical vessel pressure vs. hydrostatic pressure. As the uterus relaxes, back flow may occur. Previous work showed that DCC produced an increase in hemoglobin and hematocrit, which was no surprise but led to concerns regarding polycythemia [13,14].

In 2001, Mercer reviewed the effects of DCC [15]. In the studies reviewed, cord clamping was delayed by 30-45 seconds in preterm infants and from 3 to 10 minutes in term infants. When available, the author reported the placement of the infant in relation to the placenta and the use of oxytocin or similar medication after the delivery. Although DCC led to higher hematocrit levels and increased blood viscosity in infants of all gestations, DCC did not cause symptomatic polycythemia and there were no documented adverse effects. Following DCC, term and preterm infants had higher hematocrits at 2 months and a trend toward increased ferritin levels. Most reviewed trials did not show a significant increase in bilirubin levels in both term and preterm infants exposed to DCC. In addition DCC led to greater pulmonary and systemic vasodilatation and increased

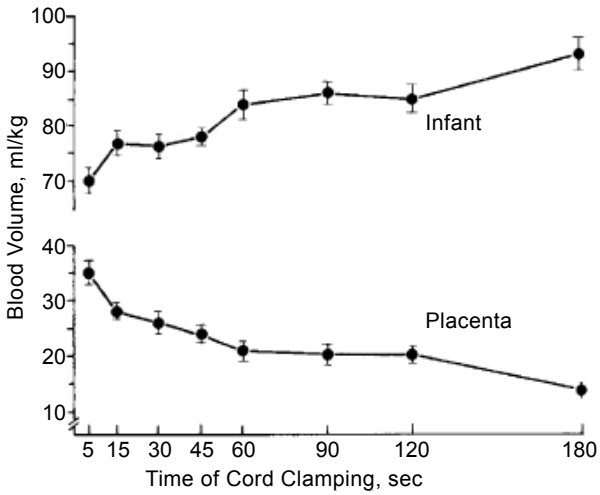

Figure 1: Relation between infant's blood-volume and placental residual blood-volume at various times of cord clamping. Reprinted from the Lancet,2;87: Yao et al, Distribution of blood between infant and placenta after birth.871-3, Copyright (1969), with permission from Elsevier.

***Corresponding author:** Amitai Kohn, MD, Department of Neonatology, Beaumont Children's Hospital, 3601 W.13 Mile Road, Royal Oak, MI 48073, USA; Tel: 248-898-0633; Fax: 248-898-3393; E-mail: Amitai.kohn@beaumont.edu

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perfusion of the brain, body, and intestines in term and preterm infants. Improved blood pressure, oxygen carrying capacity, urine output, and temperature were also noted. No immediate harms were identified with DCC.

In this review I will attempt to summarize the multiple meta-analyses and controlled trials performed to date. I have also included data from additional non-controlled studies when they provide physiologic explanations and data that could not be obtained by randomized studies.

Term Infants

Analysis of published data is complicated by lack of an agreed upon definition of DCC which, in different studies, ranges from 2-10 minutes or until the cessation cord of pulsation following birth. ICC usually means what it says although some studies include cord clamping within 10 seconds after birth.

McDonald and Middleton conducted a Cochrane review [16] of trials of infants subjected to ICC and DCC. The DCC infants had:

(a) Higher hemoglobin levels (weighted mean difference [WMD] 2.17 g/dL; 95% CI 0.28 to 4.06; random effect model) at birth and at 24 -48 hours. The differences in hemoglobin levels disappeared by six months.

(b) Higher ferritin levels at six months (WMD 11.8 µg/L; 95%CI 4.07 to 19.53; 1 trial of 315 infants). DCC improved the infants' iron status, an important benefit where access to good nutrition is poor.

(c) Received more phototherapy-5% vs. 3% in the ICC group (Relative risk [RR] 0.59, 95% CI 0.38 to 0.92; 5 trials of 1762 infants).

(d) No difference in neonatal polycythemia

(e) No increase in the risk of postpartum hemorrhage

Table 1 summarizes the data from a meta-analysis of 15 controlled trials in full term infants [17]. DCC ranged from 2 to 5 minutes following delivery or until either cessation of cord pulsation or placental descent into the vaginal opening. 1001 infants were exposed to DCC and 911 to ICC.

These studies provide convincing evidence that DCC enhances the infant's hematologic status for the first 3months of life and enriches iron stores for up to 6 months a valuable contribution to the infants' nutrition in developing countries.

A later study compared DCC (over 3 minutes) vs. ICC (less than 10 seconds) [32]. At 4 months, the groups had no significant differences in hemoglobin concentration. DCC groups had

(a) Increased mean ferritin levels 117 µg/L vs. 81 µg/L ($p<0.001$)

(b) Decreased prevalence of iron deficiency (1 [0.6%] vs. 10 [5.7%], $p=0.01$, absolute risk reduction 5.1%, Number needed to treat =20).

(c) Decreased anemia at 2 days

(d) No differences in polycythemia or bilirubin levels requiring treatment.

In a study of Peruvian infants [33] cord clamping varied from 57 ± 32 seconds (ICC) to 107 ± 87 seconds (DCC). At 8 months, 79.1% of the ICC infants were anemic (hemoglobin 9.9 ± 1.39 g/dL) vs. 63.4% of the DCC group (hemoglobin 10.7 ± 0.9 g/dL, $p<0.05$) and lastly, in a small randomized study of term infants in a malaria endemic location in Zambia, those with DCC (after cord pulsation cessation) had a slower decline in hemoglobin for the first 4 months, although by 6 months there was no difference in hemoglobin levels [34]. It is important to mention that a hurdle in implementing DCC is the current practice of umbilical cord banking that requires early cord clamping in order to achieve larger placental blood volume and, therefore, more stem cells [35].

Obstetricians have expressed concerns regarding the reliability of cord blood values following DCC. Andersson et al. found that the umbilical cord pH and pCO_2 were not significantly different between DCC and ICC groups [36]. However, Valero J et al. reported a significant decrease in pH, oxygen saturation, glucose level, oxygen content, bicarbonate, and base excess, and an increase in lactate and pCO_2 in umbilical cord samples following DCC [37]. Nevertheless, the infants in this study were vigorous and there was no association between the clinical picture and laboratory results.

Outcome variables in DCC infants vs. ICC	Time	Number of trials	Number of infants	Reported results
Higher mean hematocrit	6 hours	2 [18,19]	494	WMD, 4.16%; 95% CI, 0.83% to 7.49%
	24-48 hours	4 [19-21]	341	WMD, 10.01%; 95% CI, 4.10% to 15.92%
	5 days	4 [21-24]	120	WMD, 11.97%; 95% CI, 8.50% to 15.45%
	2 months	1 [25]	47	WMD, 3.70%; 95% CI, 2.00% to 5.40%
Higher blood volume	2-4 hours	2 [22,26]	60	WMD, 9.07 mL/kg; 95% CI, 5.81 to 12.32
Higher ferritin level	2-3 months	2 [22,27]	144	WMD, 17.89 µg/L; 95% CI, 16.58 to 19.21
	6 months	1 [18]	315	WMD, 11.80µg/L; 95% CI, 4.07 to 19.53
Increased risk of Polycythemia	7 hours	2 [18,19]	236	RR, 3.44; 95% CI, 1.25 to 9.52
	24-48 hours	7 [19,20,22-25,27]	403	RR, 3.82; 95% CI, 1.11 to 13.21
Decreased risk of Anemia	24-48 hours	1 [19]	179	RR, 0.20; 95% CI, 0.06 to 0.66
	2-3 months	2 [25,28]	119	RR, 0.53; 95% CI, 0.40 to 0.70
No difference in mean serum bilirubin	24 hours	2 [26,29]	163	WMD, 3.81 µmol/L; 95% CI, −17.55 to 25.18
	≤ 72 hours	2 [23,29]	91	WMD, 18.27 µmol/L; 95% CI, −2.47 to 39.00
No increase risk of jaundice	24-48 hours	8 [19-24,29,30]	1009	RR, 1.35; 95% CI, 1.00 to 1.81
	3-14 days	1 [18]	332	RR, 1.27; 95% CI, 0.76 to 2.10
No increased risk for tachypnea	NA	3 [19,30,31]	296	RR, 2.48; 95% CI, 0.34 to 17.89
No increase risk for NICU admission	NA	1 [19]	185	RR, 2.02; 95% CI, 0.63 to 6.48

JAMA, 2007; 297(11): 1241-52
DCC: Delayed Cord Clamping; ICC: Immediate Cord Clamping; WMD: Weighted Mean Difference; RR: Relative Risk; NICU Neonatal Intensive Care Unit

Table 1: Summary of data from different trials comparing late with early clamping of the umbilical cord. Complied from the data of Hutton et al. Late vs. early clamping of the umbilical cord in full-term neonates systematic review and meta-analysis of controlled trials.

	4 h				24 h				72 h			
	DCC (*n*=15)		ICC (*n*=24)		DCC (*n*=15)		ICC (*n*=23)		DCC (*n*=14)		ICC (*n*=21)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Heart rate, beats per min	140.28	17.12	144.54	13.73	138.85	16.98	140.13	11.56	147.74	14.93	149.90	12.87
SaO_2, %	91.81	3.10	94.08	3.17	93.48	2.64	93.63	2.83	92.50	3.30	94.36	3.82
$PacO_2$, kPa	5.38	1.98	5.67	1.31	5.19	1.28	5.59	0.98	5.99	1.39	5.76	1.01
Mean arterial blood pressure, mm Hg	38.90*	9.34	33.56	6.53	44.20	10.89	44.50	6.63	49.69	9.65	44.48	7.79
Hematocrit, %	55.56*	8.42	50.20	7.73	55.93*	7.19	49.74	8.34	55.17*	7.56	48.14	7.24

*Significantly different compared with the control group (P<.05) by Mann-Whitney *U* test

Table 2: Clinical data following delayed cord clamping. Adopted from Baenziger O, Stolkin F, Keel M, von Siebenthal K, Fauchere JC, et al. (2007) The influence of the timing of cord clamping on postnatal cerebral oxygenation in preterm Neonates: A randomized, controlled trial. Pediatrics 119: 455-459.
DCC: delayed cord clamping. ICC immediate cord clamping.

In their review, the committee on obstetric practice of the American College of Obstetricians and Gynecology's notes both the potential benefit of DCC in term infants born in areas where iron deficiency is prevalent, and the increased risk of hyperbilirubinemia requiring phototherapy [38].

Preterm Neonates

Following preterm births, the definition of DCC vs. ICC varies between authors. In the most recent Cochrane review [39] DCC was defined as occurring after 30 seconds although the reported range was from 30 seconds to 3 minutes. ICC occurred from 5 to 20 seconds following delivery.

During their stay in the NICU, preterm infants often receive multiple transfusions for a variety of reasons. When indicated, transfusions decrease apnea of prematurity [40,41], may decrease neurologic adverse effects [42], and improved cerebral oxygen delivery, which may improve neuro developmental outcome [43]. DCC may also decrease the need for neonatal transfusions. On the other hand, because preterm neonates often require immediate resuscitation, stabilization, and temperature management, implementing DCC in this population is a challenge.

Mercer et al. conducted a randomized controlled trial of DCC (30-45 seconds) vs. ICC (5-10 seconds) in infants <32 weeks gestation [44].

No differences were found in the incidence of Bronchopulmonary Dyplasia (BPD) or Necrotizing Enterocolitis (NEC) the primary outcome variables, but there were significant differences in the secondary outcomes, Intraventricular Hemorrhage (IVH) of all severities and Late Onset Sepsis (LOS). The DCC group had:

(a) Less IVH of all grades in the first 28 days, five cases [14%] vs. 13 [36%] (p=.03, OR =3.5 95% CI 1.1-11). Most infants with IVH were ≤ 30 weeks gestation. Interestingly, the protection against IVH was particularly marked in male infants after DCC (2 [9%] vs. 8 [42%], p<0.05). Multivariate analysis of the impact of DCC vs. ICC on IVH found OR of 3.5 (95% CI: 1.1-11.1) for the incidence of IVH with ICC.

(b) Less blood culture-proven sepsis (3% vs. 22%; p=.03).

The male advantage that apparently resulted from the receipt of additional blood volume may be gender-specific for neuro-protection and immuno-protection effects. Gender specific protection against the development of IVH has also been documented in males exposed to prophylactic treatment with indomethacin [45]. At7 months, males in the DCC group scored higher than those in the ICC group in the motor Bayley Scales of Infant Development [46]. This could reflect improved cerebral oxygenation following DCC. In a small study of 39 preterm infants, Baezinger et al. assigned 15 to DCC (60-90 seconds) and 24 to ICC (within 20 seconds) and evaluated the effect of DCC on cerebral oxygenation. They measured deoxyhemoglobin (μM), oxyhemoglobin (μM), total hemoglobin (tHb; μM), and regional tissue oxygen saturation (StO_2; %) by near-infrared spectroscopy and collected additional clinical data at 4, 24, and 72 hours. The results of this study are shown in table 2 [47].

The increase in StO_2; % and oxyhemoglobin values at the age of 4 hours might account for the observed decrease in IVH and improved neuro developmental outcomes. There was no change, however in cerebral blood volume.

Rabe et al. conducted a Cochrane review of 738 infants of gestational age 24-37 weeks. The maximum delay in cord clamping was 180 seconds. The DCC group had:

(a) Fewer transfusions (7 trials, 392 infants RR 0.61, 95% CI 0.46 to 0.81).

(b) Less IVH (of all grades) (10 trials, 539 infants RR 0.59, 95% CI 0.41 to 0.85).

(c) Lower risk for NEC (5 trials, 241 infants, RR 0.62, 95% CI 0.43 to 0.90).

(d) Higher peak bilirubin levels (7 trials, 320 infants, mean difference 15.01 mmol/L, 95% CI 5.62 to 24.40).

There were no differences in deaths before or after discharge, IVH of grades 3 or 4, periventricular leukomalacia, and neurosensory disability at the age of 2-3 years [39].

Meyer and Mildenhall evaluated the hemodynamic status of preterm <30 weeks gestation by measuring the Superior Vena Cava (SVC) blood flow within 24 hours after DCC and ICC. The median SVC flow was significantly lower in the ICC group compared with the DCC group (p=0.028), and the only infants with IVH were in the ICC group [48].

In another study, serial Doppler studies were performed on premature infants (24-31 6/7 weeks gestation). The DCC group had higher superior vena cava blood flow and, greater right ventricular output and stroke volumes at 48 hours [49]. It was reported that SVC blood flow is the best marker for upper body systemic blood flow and cerebral perfusion, which may explain the decreased IVH in premature infants who had DCC [50].

Is DCC Safe for Preterm Infants?

In a single center study, Kaempf et al. found that DCC in preterm infants had no effect on initial body temperature but these infants had higher mean systolic and diastolic blood pressures, higher 1-minute Apgar scores, and required less delivery room resuscitation. DCC did not decrease the need for transfusion, and no other significant

findings were reported [51]. Aziz et al. showed that it was possible to implement DCC in infants <33 weeks gestation with meticulous attention to education and reinforcement [52].

The Effects of Delayed Cord Clamping on the Mother

There is a paucity of data regarding the effects of DCC on the mother. In 59 term infants the cord was clamped immediately after delivery (range 0 to 9 seconds) and in 58 at 4.5 (range 1.5-11) minutes [53]. Total post partum blood loss in the ICC mothers was 133ml vs. 67 in the DCC group ($p<0.01$).

In their literature review McDonald and Middleton did not find an increase in risk for PPH when the umbilical cord was left unclamped for two minutes [16].

Andersson et al. found no significant increase in PPH, need for transfusion or the length of the third stage of labor in 193 mothers when DCC was compared with controls [36].

Summary

The debate over the optimal timing of umbilical cord clamping has lasted half a century and has been addressed in a multitude of clinical trials, experience in single centers, and reviews. The preference for ICC is based on established obstetrical practice, personal preference, expert opinion, and concerns regarding postpartum hemorrhage although both older and more recent studies have shown no effect of ICC or DCC on postpartum hemorrhage. From a neonatal and teleological perspective, it seems unlikely that parturition was intended to deprive either the term or preterm newborn of the placental blood and there is considerable evidence that the placental transfusion conveys important short- and long-term benefits in the newborn and, in particular, the vulnerable preterm infant. The risk of clinically relevant adverse effects for the mother or infant is small. The simple intervention of allowing some placental transfusion to take place can decrease IVH and NEC, shorten hospital stays, and improve the long-term neuro developmental outcome for infants in our NICUs. In limited resource countries, DCC in late preterm and term infants contributes to their nutrition, and diminishes the risk of later anemia.

Obstetricians and neonatologists need to develop a consensus for cord clamping in term and preterm infants that will allow the placental transfusion to occur. A rigorous educational program for the entire staff must follow the establishment of an agreed-upon protocol. In addition, ongoing data collection is necessary to demonstrate that this practice leads to more benefits than harms.

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