Neonatal Outcome Following Cord Clamping After Onset of Spontaneous Respiration

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**WHAT’S KNOWN ON THIS SUBJECT:** Delaying cord clamping beyond 30 to 60 seconds after birth seems beneficial for all infants due to blood transfusion from placenta. Experimental data have demonstrated that ventilation implemented before cord clamping improved cardiovascular stability by increasing pulmonary blood flow.

**WHAT THIS STUDY ADDS:** Healthy self-breathing neonates in a low-resource setting are more likely to die if cord clamping occurs before or immediately after onset of spontaneous respirations. The risk of death/admission decreases by 20% for every 10-second delay in clamping after breathing.

**KEY WORDS**
cord clamping, neonatal mortality and morbidity

**ABBREVIATIONS**

BW—birth weight
CC—cord clamping
CI—confidence interval
DCC—delayed cord clamping
ECC—early cord clamping
FHR—fetal heart rate
GA—gestational age
OR—odds ratio
SR—spontaneous respirations

Dr Ersdal conceptualized and designed the study, oversaw data collection, carried out the initial analyses and interpretation, and drafted the initial manuscript; Drs Linde and Auestad contributed to data analysis and interpretation and reviewed and revised the manuscript; Dr Mduma contributed to design of the study, coordinated and supervised data collection, and reviewed and revised the manuscript; Dr Perlman contributed to the design of the study and to data analysis and interpretation and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

The external funding source had no role in study design, data collection, data analysis, data interpretation, writing of the report, or in the decision to submit the paper for publication. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

All authors had no other financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years or no other relationships or activities that could appear to have influenced the submitted work.

doi:10.1542/peds.2014-0467

Accepted for publication May 7, 2014

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Umbilical cord clamping (CC) and subsequent cutting are routine procedures performed at all facility-based deliveries, but the optimal time for clamping remains unclear. After decades with focus on immediate or early cord clamping (ECC), the past 15 years have seen a shift toward delayed cord clamping (DCC). This issue has provoked intense international debate and is further complicated from a lack of what defines both ECC and DCC. ECC has been described as CC performed from <10 seconds and up to 60 seconds postdelivery, whereas DCC is defined as CC performed after 30 to 60 seconds or extending up to 2 to 3 minutes of birth, and/or after cessation of pulsations in the cord. Accumulating evidence suggests that CC beyond 30 to 60 seconds after birth is of benefit for most infants.1–7

Observational studies in the 1960s and 1970s suggested an association between DCC and overtransfusion of the infant, causing polycythemia, hyperbilirubinemia, and respiratory symptoms.8–10 Other studies indicated that ECC prevented placental transfusion and resulted in more respiratory distress syndrome among preterm infants.11–13 Importantly, in settings with a high prevalence of HIV infection, immediate CC has been thought to reduce the risk of mother-to-child transmission. Furthermore, active management of third-stage labor, including use of oxytocin, together with ECC within 30 to 60 seconds and controlled cord traction, is considered important in the prevention of postpartum bleeding.14 However, a recent systematic review found no difference in maternal blood loss with varying time of CC, but a decreased need for neonatal blood transfusions was noted with DCC.4

Indeed the renewed interest in the timing of CC is in part directed at preventing the need for donated blood transfusions by increasing the placental transfusion of red blood cells to the newborn and thereby reducing the risk of anemia and iron deficiency for all newborns.1–7 This is particularly important in developing countries where anemia during infancy and childhood is highly prevalent. Additionally, for preterm infants, DCC has been shown to increase systemic blood pressure.1 However, Rabe et al have reported higher rates of phototherapy and clinical jaundice with DCC.15 Interestingly, a recent experimental study demonstrated that positive pressure ventilation before CC in preterm lambs improved cardiovascular function and stability by increasing pulmonary blood flow, supporting the concept of DCC.16

The aim of this study is to determine the optimal time for CC in a population of self-breathing neonates in relation to the initiation of SR and to 24-hour neonatal outcome including death and continued medical problems in a low-resource setting.

METHODS

This is an ongoing descriptive observational study initiated in November 2009 at Haydom Lutheran Hospital; a rural referral hospital in northern Tanzania. Haydom provides comprehensive emergency obstetric care and basic emergency newborn care to a population of ~500 000 people.18 Midwives largely conduct deliveries with doctors on call 24 hours. The current hospital guideline for CC is to wait 1 to 3 minutes if the infant is breathing, consistent with the most recent World Health Organization recommendation.19

Research assistants/observers are continuously present in the labor ward, working in shifts. Three observers cover each shift; 2 are always located in the delivery room or in the theater; 1 covers an adjacent neonatal area.17 Time intervals from birth to initiation of SR and CC are timed using stopwatches. The findings are recorded on a data collection form and include labor information and fetal heart rate (FHR) measurements, neonatal characteristics and interventions in the delivery room, and perinatal outcome within 24 hours (normal, admitted to neonatal unit, death, or stillbirth; Appendix 1). The research assistants also review the partograms that are filled out by the birth attendants.

For this report, the data collection was from November 2009 through January 2013. After birth, infants who required more than routine care (eg, prolonged resuscitation, difficulties with breathing or feeding, prematurity) were triaged to the neonatal area with the capability of providing intravenous fluids and antibiotics and were intermittently cared for by family members and the labor staff.

Gestational age (GA) was based on self-report of the last menstrual period and distance from symphysis pubis to fundus on admission. Normal term GA at Haydom Lutheran Hospital is routinely defined as ≥36 weeks. Normal outcome was defined as survival >24 hours without detected difficulties. Intrapartum death/fresh stillbirth was defined as an Apgar score of 0 at both 1 and 5 minutes with intact skin and suspected death during labor/delivery. The study was approved by The National Institute for Medical Research in Tanzania and The Regional Committee for Medical and Health Research Ethics in Norway.

Statistical Analyses

Analysis has been performed by using Statistical Package for Social Sciences 22 and R.20 Descriptive statistics were used to present data as mean ± SD unless as otherwise stated. χ² calculations and
independent-sample t tests were used to compare subpopulations. To describe the association between CC relative to SR (time interval between initiation of SR and CC) and neonatal outcome, multiple logistic regression modeling was used. The significant associated explanatory variables were identified after stepwise forward and backward variable selection, including pregnancy complications (no versus yes), labor complications (no versus yes), FHR (normal versus abnormal), time-interval to initiation of SR (in seconds), BW > 2500 g, GA (≥34 weeks), pregnancy complications (no versus yes), labor complications (no versus yes), FHR (normal versus abnormal), time-interval to initiation of SR (in seconds), the BW and GA (≥34 weeks), and time interval between initiation of SR and CC (in seconds). The final models showed satisfactory fit according to the Hosmer-Lemeshow statistic. Odds ratios (OR), 95% confidence intervals (CI), and P values are reported.

RESULTS
The cohort comprised 15,563 infants of BW ≥ 2500 g and GA ≥ 36.4 weeks. Of these, 12,780 initiated SR and received only routine care, 12,730 (99.7%) were classified as normal 24 hours after birth, 31 (0.2%) died, and 19 (0.1%) remained in the neonatal area (Fig 1). Mean time to initiation of SR was 10.8 ± 16.7 seconds with a median time of 5 seconds. The mean time to CC was 63 ± 45 seconds, with a median time of 34 seconds. This included 60% clamped within 1 minute, 90% within 2 minutes, 98% within 3 minutes, and 2% beyond 3 minutes after birth.

The population descriptors in relationship to outcome are shown in Table 1. In all instances, complications (ie, pregnancy and labor, including cesarean delivery) and abnormal FHR were more frequently recorded in infants who died or remained admitted versus normal infants. The BW and GA of infants who died/remained admitted were significantly less than those of normal infants. Time to initiation of SR was delayed among infants who died/remained admitted versus normal, and CC occurred earlier among dead/remained admitted versus normal infants.

The neonatal outcome at 24 hours in relation to time to CC relative to the onset of SR is shown in Table 2. For the total cohort, infants who had the CC before onset of SR were more likely to die/remain admitted versus infants who started SR before CC, that is, 9 of 639 versus 38 of 12,088, respectively (OR = 4.53, 95% CI: 1.92–9.58, P = .0005); 53 cases were not valid because of missing time to start SR or to CC.

Within the cohort, 11,967 (93.6%) were of BW ≥ 2500 g. Outcome included 11,949 (99.8%) normal, 7 (0.1%) dead, and 11 (0.1%) admitted (Fig 1). The mean time to CC and SR was 64 ± 45 and 10.7 ± 16.1 seconds, respectively. Table 3 presents population descriptors in relationship to outcomes among infants of BW ≥ 2500 g, which parallel the findings for the entire cohort. Within the cohort, 813 (6.3%) infants were of BW < 2500 g of whom 881 (97%) were healthy, 24 (3.0%) died, and eight (1.0%)...
remained admitted (Fig 1). In these infants, CC occurred 8.1 seconds earlier than those of BW ≥2500 g: 56 ± 42 vs 64 ± 45 seconds, respectively (P ≤.0005).

Table 4 presents population descriptors in relationship to outcomes among infants of BW <2500 g, which also parallel the findings for the entire cohort.

**RELATIONSHIP OF CC TO THE ONSET OF SR**

To investigate the possible effects of CC relative to onset of SR on outcome ie “normal” versus “dead/admitted,” the difference between time to initiation of SR and time to CC was introduced as an explanatory variable in logistic regression models. The zero of this variable indicates SR and CC at the same time, negative values indicate CC in seconds before SR, and positive values CC in seconds after SR. After stepwise variable selection, BW (≥2500 vs <2500 g), GA (≥34 vs <34 weeks), FHR (normal vs abnormal), and pregnancy complication (yes vs no) were included to adjust for confounding effects. In further logistic regression analyses, the length of the time interval between CC and SR showed no significance when CC occurred before the onset of SR (P = .76) for both BW groups (≥2500 and <2500 g). This indicates a constantly higher risk of “death/admitted” when CC occurred before SR, an effect largely attributable to the relationship of CC preceding the onset of SR (Fig 2). Infants of BW <2500 versus ≥2500 g were more likely to die or remain admitted when CC occurred before initiation of SR (OR = 5.6; 95% CI: 2.3–13.7, P = .0001; Fig 2, Table 2).

A significant time dependency was noted when CC was performed after onset of SR (OR = 0.977, 95% CI: 0.965–0.991, P = .0007), that is, the risk of “death/admission” decreased the longer the time difference from SR to CC up to 2 minutes (Table 2, Fig 2). The risk declined at the same rate in both BW groups (Fig 2). The latter results were derived from fitting a model with constant time interval effect before zero and effect dependent on length of time interval after zero (ie, CC in seconds after onset of SR). In summary, the logistic regression analysis adjusting for BW, GA, FHR, and pregnancy complications indicated that the OR for “death/admitted” decreased by 20% (95% CI: 9%–30%) for every 10 seconds delay in CC after initiation of SR up to 2 minutes (Fig 2).

**DISCUSSION**

The data in this report describe for the first time the time relationship of CC to the onset of SR and early neonatal outcome. Infants who had their cord clamped before the initiation of SR were more likely to die or exhibit early medical issues after delivery. Conversely the risk of death and/or admission decreased to a minimum if CC was delayed for ≥2 minutes after initiation of breathing, an effect independent of BW, GA, FHR, and pregnancy complications.

During fetal to neonatal transition, several important physiologic cardiopulmonary...
changes occur, which appear to be modulated by the timing of CC (Fig 3). At birth, the fetal circulation is characterized by right-to-left shunts because of (1) the low vascular resistance in the placenta receiving 30% to 50% of fetal cardiac output, causing a low systemic pressure in the receiving 30% to 50% of fetal cardiac output, probably arterial pressures were detected, probably because the placenta with its low vascular resistance was removed from the neonatal circulation. Importantly, interrupting the venous return from the placenta before ventilation, with minimal pulmonary blood flow, reduces blood flow to the left atrium and, combined with the increased afterload, eventually decreases the cardiac output. However, if CC was performed after lung aeration in newborn lambs, a marked increase in pulmonary blood flow occurred, and the immediate hemodynamic changes were mitigated. This supports the long-standing clinical observations by Redmond et al who suggested that the first breath triggers dilatation of the pulmonary vascular bed into which blood can flow from the placental circulation if the umbilical cord is left open. An increase in pulmonary blood flow will accordingly increase venous return from the lungs to the left atrium and maintain left ventricular pressure and cardiac output and thereby systemic blood pressure. Consequently, right-to-left shunting across the ductus arteriosus and foramen ovale will decrease and reverse, resulting in increased blood flow through the pulmonary arteries. Any delay in CC beyond the onset of SR is therefore likely to be of great importance in modulating immediate cardiopulmonary transition and preventing hemodynamic instability at birth, as suggested by the experimental studies.

The findings in this report are consistent with these observations. Thus, half of the deaths and/or medical issues in the spontaneously-breathing newborns ensued if CC was performed before or few seconds after onset of SR. Furthermore, this risk decreased rapidly if CC was performed ≥10 seconds after initiation of SR. An interesting observation is that the risk of adverse outcome did not show any time relationship when CC preceded SR, that is, the risk was consistently higher (OR = 4.48). This strongly points to the importance of lung expansion and dilatation of the pulmonary vascular bed in facilitating blood transfusion from the placenta.
It is important to note that the time interval to SR was delayed among infants who died or who were admitted. However, based on the statistical modeling that included several covariates (BW, GA, FHR, labor complication, pregnancy complication, time to start SR, and time interval between CC and SR), the time to initiation of SR after birth was not related to either death or medical issues, suggesting that these infants were born with sufficient oxygen reserve and/or a well-functional placenta and umbilical cord venous flow, providing them with oxygenated blood. It is conceivable that some infants could have had shallow breathing patterns not detected by the observers.

An important observation is that death and medical admission was significantly more likely to occur in infants of low BW and GA, with 60% of the deaths and medical admissions noted in this group. Definition and calculation of GA in this rural area is inaccurate, thus selecting infants of BW $\geq 2500$ g was considered to be more reliable for analysis. Apparently strong and healthy infants of BW $<2500$ g had a 5.6-fold higher OR for adverse outcome if CC was performed before onset of SR compared with infants of BW $\geq 2500$ g. However, the risk declined at a comparable rate when CC was performed after SR in the 2 groups.

These cumulative observations support the theory of a smoother cardiovascular transition and hemodynamic stability when CC is delayed, allowing lung aeration, increasing blood flow through the lungs and thus venous return to the left atrium. This likely sustains left cardiac output and stabilizes systemic pressure and flow when the placental circulation is removed. In addition, avoidance of large hemodynamic swings may reduce the risk of intraventricular hemorrhage, especially among premature infants. In 2010, the International Liaison Committee on Resuscitation recommended a delay in umbilical CC for at least 1 minute after birth in neonates not requiring resuscitation, and the World Health Organization states “that in term or preterm infants who do not require positive pressure ventilation, the cord should not be clamped earlier than one minute after birth.” These recommendations are based on the described benefits of blood transfusion from placenta; however, we speculate that there is a combined effect of smoother cardiovascular transition, hemodynamic stability, and blood transfusion when CC occurs after onset of breathing.

A limitation of this study is the lack of specific information about causes of admission to the neonatal area and/or death. Admitted neonates were cared for by midwives and family members, occasionally a doctor, with oxygen saturation as the only parameter monitored and a limited capacity for analysis of blood samples. Therefore, specific diagnoses were difficult to obtain. It is also unclear if ECC was performed in neonates who seemed depressed or “sick” to the provider, in anticipation of moving the newborn to the resuscitation area if clinically indicated. However, only a few neonates were assigned an Apgar score $<7$ at 1 (0.3%) and 5 (0.03%) minutes, and none received any kind of assistance beyond routine care at birth (ie, drying, clean cord cutting, and maintaining warmth). They were all allowed to initiate SR without being stimulated or suctioned, indicating that the midwives considered these infants as “strong and healthy.” Additionally, labor complications, FHR abnormalities, and time to initiate SR did not influence outcome when subjected to logistic modeling, indicating a negligible problem of birth asphyxia in the cohort. Furthermore, in this rural setting, the midwives have practiced immediate or ECC for decades because of concern of mother-to-child transmission of HIV, so it is likely that ECC is a well-established habit of older midwives.

CONCLUSIONS

Apparently healthy spontaneously breathing neonates are more likely to die or be admitted if CC is performed before or immediately after onset of SR. This increased risk is not related to
duration of time between CC and SR but rather to the intervention CC that preceded SR. Conversely the risk decreased by 20% for every 10 seconds up to 2-minute delay in CC after onset of SR. These cumulative observations support the experimental findings of a smoother cardiovascular transition when CC is performed after initiation of ventilation.

ACKNOWLEDGMENTS

This study was made possible by the help of research assistants, data quality controllers, data clerks, and the health providers working at Haydom Lutheran Hospital. We thank the Hospital Management for their approval and collaboration, Erling Svensen (Centre for International Health, University of Bergen) for his help with data collection, and the Laerdal Foundation for Acute Medicine for their financial support.

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### APPENDIX 1 Information Recorded on the Data Collection Form

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<th>Labor information</th>
<th>Neonatal information</th>
<th>Perinatal outcome at 24 h postpartum</th>
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<tbody>
<tr>
<td>Antenatal care</td>
<td>Pregnancy</td>
<td>Maternal infections</td>
<td>Gender</td>
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<td>Yes or no</td>
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<td>BW (Grams)</td>
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<td>Yes or no</td>
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<td>GA (Weeks)</td>
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<td>Maternal infections</td>
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<td>Apgar scores 1 and 5 minutes</td>
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**Labor information**

- **Fetal presentation**: Cephalic, breech, shoulder dystocia, transverse, or other
- **FHR**: Normal: 120 to 160 beats/min
  - Abnormal: <120 or >180 beats/min
  - None detected or not measured
- **Mode of delivery**: Spontaneous vaginal delivery, caesarean delivery, assisted breech delivery, and vacuum extraction
- **Labor complication**: Prolonged labor; obstructed labor; preeclampsia, eclampsia, uterine rupture, hemorrhage, and cord prolapse

**Neonatal information**

- **Transitional newborn adaptation**: Time intervals (s) from birth to initiation of spontaneous respirations and cord clamping
- **Gender**: Male or female
- **BW (Grams)**
- **GA (Weeks)**
- **Apgar scores 1 and 5 minutes**
- **Interventions in the delivering room**
- **Specific observations**
  - Newborn heart rate present or not, time interval (s) from initiation of BMV to the onset of spontaneous breathing or death

**Perinatal outcome at 24 h postpartum**

- **Normal**: Survival >24 h without any detected difficulties
- **Admitted**: Designated neonatal area
- **Death**: Macerated = antepartum or fresh = intrapartum

*BMV = bag mask ventilation.*
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