CONFIDENTIAL

IS DELAYING CLAMPING OF THE UMBILICAL CORD AT THE TIME OF DELIVERY BENEFICIAL FOR EXTREMELY LOW BIRTH WEIGHT (ELBW) INFANTS?

PROTOCOL

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William Oh, MD and Avroy Fanaroff, MD

Summary/Abstract

Objective

The purpose of this Pilot study is twofold: 1) To test the feasibility of performing a randomized unmasked controlled trial to vary the timing of cord clamping at the time of delivery of an ELBW infants and 2) To test the hypothesis that delaying the clamping of the cord for 30-45 seconds at the time of birth will result in a relative increase of hematocrit of ELBW infants by 10 % when compared with those clamped within 5 seconds after birth.

Methods and Design

This pilot study will be performed in 4 centers within the NICHD Neonatal Research Network (Brown, Case Western, Cincinnati and Alabama). Infants with a gestational age of 24.0- 27 6/7 weeks gestation (by best obstetric estimates) will be eligible for the study. With permission from the attending obstetrician and neonatologist, informed consent will be obtained from the parent(s). Infants will be randomized into an early or late cord clamping group. In the early cord clamping group, the cord will be clamped within 5 seconds after the delivery of the buttocks. For the late clamped group, the cord will be clamped between 30-45 seconds after the delivery of the buttocks. Resuscitation procedure and subsequent management of the infants will be at the discretion of the physician delivering the babies and the attending neonatologists. Both vaginal and c-section deliveries will be included. Twins and mothers with third trimester bleeding (Abruptio placenta, placenta previa) will be excluded. The position of the infants prior to cord clamping will be kept as standardized as possible. The babies will be kept at about 10 inches below the birth canal in the case of the vaginal delivery and at approximately 10 inches below the level of the incision in those born by cesarean section. The primary outcome variable will be venous or arterial hematocrit at four hours of age. Secondary outcome variables will include hourly mean arterial blood pressure and need for volume expanders, blood transfusions and vasopressors during the first 12 hours, amount and frequency

of blood transfusion during infants' hospital stay, and diagnosis of sepsis, NEC, BPD, CLD and IVH as recorded in the GDB.

Sample Size

Using the hematocrit as the primary outcome variable and an expected 10% relative increase in the hematocrit by late cord clamping (two tail, 90% power) we estimated a need for a sample size of 16 infants in each arm.

Availability of study population and estimated time of protocol completion

According to 1997 GDB, the four centers have a total of 237 infants who were between 24 and 28 weeks of gestation. Assuming a 40 hour study window (requiring the presence of the research personnel) and a 50% consent rate, we will need one year to complete the study.

Feasibility of the Study

We will set up criteria to assess the feasibility of the protocol as outlined in the protocol.

Statement of the Problem

The practice of cord clamping in the ELBW infants may have significant impact on their clinical outcomes. Delayed cord clamping will result in an additional amount of placental transfusion, which will increase the infants' blood volume and arterial blood pressure. The higher mean arterial blood pressure may improve autoregulation of cerebral blood flow and reduce the potential occurrence of hypoxic/ischemia episodes that will in turn reduce the risk of IVH. The additional placental blood transfusion will also provide an increased amount of stem cells and cytokines that could enhance the immune status and reduce the incidence of neonatal infection. Additional blood volume may also reduce the need for blood transfusions during the neonatal period. The practice of cord clamping in this high-risk group of infants is not uniform among obstetricians because evidence to support the alternative practice (early or late cord clamping) is lacking. Thus, it is relevant to design a control trial that will provide evidence for setting a standard of practice.

During the Protocol Review Committee process, the reviewers rightly pointed out the significant problem of the feasibility of the intervention, i.e. the obstetrician may not agree to delay cord clamping for 30-45 seconds because of the desire to quickly hand over the ELBW infants to the neonatologist for resuscitative measures. In a survey conducted among the 14 centers, 13 indicated that the current practice is for immediate cord clamping. However, they all indicated that the intervention of delayed cord clamping as described in this protocol is

feasible. Nevertheless, we are proposing a pilot randomized, unmasked clinical trial to:

- Assess the feasibility of the intervention

- Confirm the acute effect of placental transfusion in the delayed cord clamping group, i.e. significant increase in hematocrit during the first four hours of life.

Hypothesis

Our primary hypothesis is that compared with those infants, in whom the umbilical cord is clamped immediately (within 5 seconds of birth); ELBW infants with delayed cord clamping (between 30-45 seconds of birth) will have higher hematocrits at 4 hours of age.

The secondary hypothesis is that delayed cord clamping will be associated with:

- Higher arterial blood pressure during the first 12 hours of life
- Less need for volume expansion and pressor therapy during the first 24 hours of life
- Less need for blood transfusions during hospitalization and at status

The incidence of death or severe IVH/Periventicular leukomalacia (PVL) and nosocomial sepsis will be collected for future reference in the event that a larger definitive study were planned; the assumption is that the pilot study will show positive results from the stand points of feasibility and acute effects of placental transfusion in this high risk group of infants.

Specific Aims

1) Identify a group of eligible subjects, i.e. those who are 24.0 -27 6/7 weeks of gestation.
2) Implement an intention to treat randomized unmasked trial with varying cord clamping time [early - immediately after the delivery of the infants buttock (< 5 seconds) and late- cord clamping at 30-45 seconds after the delivery of the infant's buttock.

Evaluation of Feasibility

The feasibility of the protocol will be judged based on the following: 1) The enrollment rates of the eligible infants during the study period; 2) Of those who were eligible and were not enrolled, what percentage were due to obstetrician's refusal to adhere to the infant's grouping (particularly with reference to delayed cord clamping) and 3) Of those randomized to delay cord clamping, what percentage ended up not clamped at the designated time because of the obstetrician's concern for the infants' condition.

Rationale/Justification

As described below, the trial is justified because there are no definitive data to support the practice of cord clamping with reference to timing. If the hypothesis of our pilot study is verified, it could provide the basis for planning a larger trial to justify a specific practice (delayed cord clamping) with beneficial outcomes.

Background /Previous Studies

Placental transfusion as a result of delayed cord clamping at birth is a well-known phenomenon. When clamping of the umbilical cord is delayed for three minutes in term infants during a vaginal delivery, the infant will receive approximately 25% more blood volume from the placenta (1- 5). This extra amount of blood volume will result in several physiological changes: higher systemic blood pressure (6), higher renal blood flow (7), lower lung compliance, (because of active translation of the fluid portion of the blood from the intravascular into the extravascular (interstitial) spaces (8) with subsequent hemoconcentration and an increase in hematocrit (9). In preterm LBW infants, placental transfusion also results in higher blood volumes and hematocrit (10,11). The study by Kinmond et al (11) also showed no respiratory complication and the infants with delayed cord clamping had fewer needs for transfusion. Usher also showed that preterm infants, who received placental transfusion and developed respiratory distress syndrome, had better outcome than those who did not receive placental transfusion (12).

More recently, there were three studies from Europe that document the effects of delayed cord clamping in very low birth weight (VLBW) infants. In one study (13) in VLBW infants delayed cord clamping of 45 seconds after vaginal delivery results in no difference in Apgar scores and need for mechanical ventilation, but fewer infants had mean arterial blood pressures of < 30 mm Hg. In another study, (14) late clamping of the cord (30 seconds) following cesarean section, and with the infants placed below the level of the placenta, resulted in higher MABP, systemic vascular resistance and hematocrit which suggests that in cesarean sections, placental transfusion does occur provided the infant is placed below the level of the placenta. In a third study (15) delayed cord clamping (> 30 seconds resulted in higher blood volume for both vaginal and cesarean section delivery. All three investigators concluded that delayed cord clamping is a safe procedure in preterm VLBW infants and may have beneficial effects in the circulatory adjustment of these infants during the immediate postnatal life.

The increase in blood volume may improve circulatory status, with less need for volume expansion to maintain normal perfusion. The higher mean arterial blood pressure is also an important physiologic observation because of its potential

effect on the autoregulation of cerebral blood flow. The latter is relevant in the pathogenesis of intraventricular hemorrhage (IVH). The exact mechanism of IVH is currently unknown. However, the most likely theory has to do with loss of autoregulation and the subsequent fall in blood pressure and cerebral perfusion that leads to cerebral ischemia/hypoxia and reperfusion and subsequent bleeding in the germinal matrix and IVH. It is known that the level of mean arterial blood pressure is directly related to the range of MABP at which the autoregulation of cerebral blood flow is maintained (17,18). If placental transfusion results in an increase in MABP which in turn may widen the range of MABP, we can speculate and hypothesize that it will be less likely for these infants to develop hypotension induced reduction in cerebral blood flow and less incidence of IVH. A recent study by Hofmeyr et al (19) addressed this issue. They did a randomized controlled trial with 86 infants (BW less than 2,000 GM) into immediate (n=40) and delayed cord clamping (n=46) groups. They found no difference in the incidence of IVH between the two groups (8/40 in the immediate cord clamping and 11/46 in the delayed cord clamping group, OR .80, 95% CI .29-2.2). However, they commented that the sample size was too small for the event rate and suggested that further studies are required. Furthermore, the study populations were of higher birth weight and this is likely the reason for a lower event rate and larger required sample size.

Since VLBW infants often require multiple blood sampling for laboratory analysis to guide clinical management which necessitates subsequent blood transfusion, one can also anticipate that the extra amount of blood transfused from the placenta as a result of delayed cord clamping could provide the reserve of blood volume and reduce the need of subsequent blood transfusion.

It has also been shown that cord blood contains a large amount of cytokines and stem cells (20). The amount of cytokines and stem cells are inversely proportional to gestational age (21-24). Thus, another potential benefit of allowing an extra amount of placental blood to be transfused to the VLBW infants, is the availability of these immune related cytokines and stem cells that could provide immunologic protection for early onset as well as late onset neonatal sepsis in this group of high-risk infants.

Methods and Procedures

In regards to the feasibility of the study, McDonnell and Henderson-Smart (16) have shown that delayed cord clamping in preterm delivery is feasible. However, their study did not confirm the expected difference in hematocrit and suggested that it may be necessary to either prolong the clamping time to greater than 30 seconds or place the infant below the introitus or uterus prior to cord clamping. We surveyed the centers to assess 1) current practice of timing of cord clamping and 2) willingness of the MFM groups to perform the specified timing of cord clamping for each of the two study groups. The result (data attached) showed that of the 11 centers which responded, all performed early cord clamping and

10 felt that the study is feasible. Three centers, Cincinnati, Indiana and Tennessee did not respond to the survey.

Description of Study Design

This is a randomized unmasked controlled trial involving infants between 24.0 - 27 6/7 weeks of gestation. Since the neonatal physicians are likely to be in attendance at the delivery, logistically this will make masking the study difficult.

Study Population
Infants with a gestational age of 24.0 - 27 6/7 weeks gestation (by best obstetric estimates at birth) will be eligible for the study.

Eligibility and enrollment Criteria

- Gestation 24.0 -27 6/7 weeks
- Singleton
- Obstetrician's approval of enrollment into study
- Parental consent

Exclusion Criteria

- Obstetrician's refusal to enroll infants
- Parental refusal for consent
- Prenatally-diagnosed major congenital anomalies
- Intent to withhold or withdraw care
- Significant bleeding due to placenta previa or abruption

Study Intervention

Once the infant is eligible and physician and parental consents are obtained, the infant will be randomized into either delayed or early cord clamping group. The randomization will be done by an envelope system at each site. The research personnel, who will be in attendance at the delivery, will inform the obstetrician, in attendance, of the grouping of the infant and the study procedure (see below). To be successful in this trial, it is essential that we have the strong commitment and collaboration of our obstetricians, neonatologists and fellows. In addition to the description of the study procedure in regards to timing of the cord clamping by the obstetrician (see below), the research personnel will use a stopwatch to accurately time the cord clamping.

Study Procedure

Mode of Delivery, position of the infants and timing of cord clamping

- **Early cord clamping Group** - When the infant's buttocks are delivered (vaginal delivery), or the infant is removed from the uterus (Cesarean section), the obstetrician will clamp the umbilical cord immediately (< 5 seconds). The research personnel will use a stopwatch to record the exact timing of the cord clamping. Following the cord clamping, the obstetrician will clear the infant's airway with an appropriate suction device and use a warm towel to dry the infant. The cord is then cut and the infant is handed over to the neonatologist in attendance for subsequent care

- **Late cord clamping group** - Following the delivery of the infant's buttocks or infant from uterus, the obstetrician will clear the airway using appropriate suction device. A warm towel will be used to dry the infant's skin and care will be taken that no tension or traction is placed on the cord. At the time of these maneuvers, the infant will be placed approximately 10 inches below the mother's birth canal (vaginal delivery) or at approximately 10 inches below the level of the incision (Cesarean section). In the meantime, the research personnel in attendance, using the stopwatch, will record the time when the infant's buttocks are delivered or the infant is delivered from the uterus. She/he will then count out the time elapsed in seconds to the obstetrician while he/she is doing the suction and drying maneuvers. At 30 -45 seconds,

the obstetrician will clamp and cut the umbilical cord, and the infant is handed over to the neonatologist in attendance. If for any reason, the cord is clamped early in a late clamped group infant, the infant will be considered as a late clamped group since this is an intent to treat protocol. A protocol violation report will be made.

In both groups, in addition to the exact timing of the cord clamping, the following parameters will be collected: one and five minutes Apgar scores; blood pressure in the first 12 hours of life; vasopressor and volume expander use in the first 12 hours of life; hematocrit levels at 4 hours of age and at 2, 4, and 6 weeks of age and at status; method of ventilation at 4 hours, as well as, data related to sepsis, IVH, NEC, CLD and transfusions. The subsequent clinical management of the infants will be at the discretion of the neonatologists. No attempts will be made to dictate the clinical management of these infants.

Primary Outcome Variable:

• Hematocrit at 4 hours of age. Since most (if not all) of these infants will have an umbilical artery catheter in place, arterial blood will be used for the hematocrit measurement. The hematocrit may be done in conjunction with a complete blood count that is done by coulter counter as part of routine clinical care. In the absence of arterial lines, venous blood can be used as alternative. A capillary hematocrit is not acceptable.

Secondary Outcome variables

Arterial blood pressures by transducer connected to the infant's monitors will be collected. Data will be recorded hourly during the first 12 hours. In the absence of an umbilical artery catheter, non-invasive blood pressure measurements can be used. Data recorded will include:

- Use of volume expanders and pressor medications during the first 12 hours of life

- Amount of blood transfused- ml/kg and age of administration during the infant's stay in the NICU

- Episodes of sepsis and positive blood cultures during the infant's stay in the NICU. Data will be obtained from the infection data forms in GDB for early and late neonatal sepsis along with organism involved.

- Incidence of IVH, NEC and CLD as defined by the GDB.

- Infant's final outcome- death or discharge alive
- If the infant enrolled is > 1,500 grams, GDB data will be generated and incorporated in the cord clamping data file.

Sample Size Calculation

The primary outcome variable is hematocrit during the first 4 hours. Our GDB does not have the values for this parameter. Nelle et al (14), showed that in their study, the hematocrit of infants at 4 hours of age, with early cord clamping was 46 (4) % Mean (SD). Sample size calculations by Data Coordinating Center statisticians are listed below:

Power	% Increase in Hct by delayed cord clamping		
	10%	15%	20%
80%	24	12	6
90%	32	16	8

We will assume a modest increase of 10% and 90% power which means we will need 16 infants in each arm.

Available population and compatibility with other study protocols

In 1997, the GDB shows that there were 237 infants admitted to the four participating centers who were between 24 and 28 weeks of gestation. Assuming a 50% consent rate and a 40 hour enrollment time window because we need the presence of research personnel, the time required to complete the study will be approximately a year.

Potential Risks

Although there is the theoretical possibility that the infants with delayed cord clamping may become polycythemic or develop features of congestive heart failure, none of the published data have encountered these problems nor have the recipients of the placental transfusions encountered the problem of hyperbilirubinemia. If the skin drying procedure is done as described in the protocol, it is unlikely that hypothermia would be a problem either. Thus, we considered the risk as minimal if any.

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