

FOCUS ON NEONATOLOGY

Affiliated with Columbia University College of Physicians and Surgeons and Weill Cornell Medical College

When to Clamp the Cord in the Non-Breathing Baby Needing Resuscitation

Delaying cord clamping after childbirth has been shown to increase the amount of blood that flows from the placenta to the newborn. But what if the baby needs resuscitation? When is the best time to clamp? Researchers at NewYork-Presbyterian Hospital/Phyllis and David Komansky Center for Children’s Health want to find out. “The optimal timing of umbilical cord clamping in neonates is the hottest topic in neonatology,” asserts Jeffrey Perlman, MD, Chief of Newborn Medicine and Professor of Pediatrics at Weill Cornell Medical College, who will be leading a study to answer this question.

Umbilical cord clamping is typically performed within 15 to 20 seconds after birth, with the infant at or below the level of the placenta. Although many randomized controlled trials of term and preterm infants have evaluated the benefits of immediate versus delayed cord clamping, the ideal timing for clamping has yet to be determined and is still a subject of debate. Some studies have shown that delaying clamping for 60 seconds increases the stability of premature infants and increases blood flow by approximately 5 percent (50 cc). Investigational data have suggested that delaying cord clamping for 30 to 60 seconds after the baby takes the first breath can smooth the transition to postnatal life. Because it is simple to implement, the technique is a way to



enhance that transition for infants born in resource-limited areas.

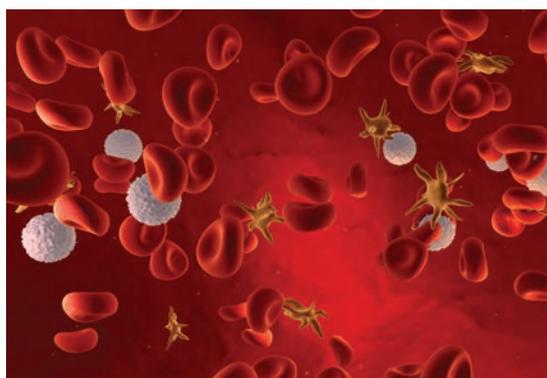
In a study Dr. Perlman and his colleagues performed in a rural Tanzanian hospital, data were recorded for over 15,000 infants born between November 2009 and February 2013. The risk of

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New Model Offers Hope for Evaluating Neonatal Antithrombotic Agents

Newborns undergoing cardiac and palliative surgeries — especially those who require the insertion of shunts — are at risk of postsurgical thrombosis. The primary agent used in neonates to reduce the risk of blood clots is aspirin. But calculating the proper dosage for an infant is not an exact science, and even with aspirin therapy, as many as one in seven newborns with shunts develops a blood clot.

While adults have benefited from a plethora of novel antithrombotic therapies, the neonatal field has not witnessed similar advances. That’s because drug companies are hesitant to conduct clinical trials of investigational anticoagulants in fragile neonates. Now an innovative model to assess platelet function, developed at NewYork-Presbyterian/Morgan Stanley Children’s Hospital,



may change that scenario by providing a system through which new anticlotting drugs for infants can be tested.

Researchers led by Thomas Diacovo, MD, Associate Attending Physician at NYP/Morgan Stanley Children’s and Associate Professor of Pediatrics and Pathology and Cell Biology at Columbia University College of Physicians and Surgeons, have developed an “avatar mouse model” which supports human but not mouse platelet-mediated thrombosis. This was accomplished by genetically modifying von Willebrand factor, which plays an essential role in coagulation. They validated the model by examining the effects of various antithrombotic agents on platelet function (*Circulation*. 2011;123:319-326) and recently generated

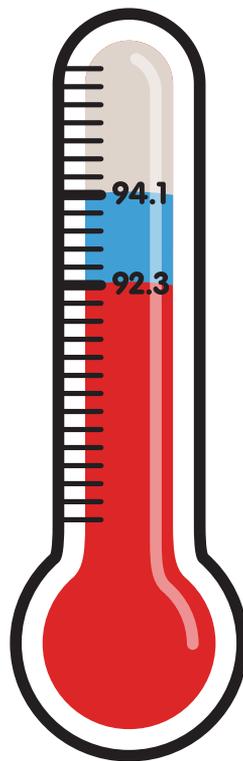
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A Cool Approach to Preventing Neonatal Encephalopathy

The American College of Obstetrics and Gynecologists calls neonatal hypothermia treatment “a medical milestone” to minimize long-term brain damage in neonatal encephalopathy. Yet the approach is effective in only about half of treated neonates. Researchers at NewYork-Presbyterian Hospital/Phyllis and David Komansky Center for Children’s Health are going back to the laboratory to identify the optimal choice of medications to be used in conjunction with neonatal hypothermia to enhance neurologic protection.

Neonatal hypothermia involves reducing a newborn’s body temperature to between 92.3° and 94.1° F (depending on the modality) for 72 hours, starting within six hours of birth by cooling just the head or the whole body. It is reserved for infants at risk of neurologic damage due to a sentinel event during labor — such as an umbilical cord abruption, placental prolapse, or significant fetal heart abnormalities — those who do not breathe on their own at birth and require intubation or aggressive resuscitation, infants with acidosis, and those with progressive signs of early neurologic changes.

At NYP/Komansky Center, newborns undergoing such “brain cooling” are put into a state of “hibernation” with midazolam (Versed®) to sedate them as well as reduce the risk of seizures and enhance brain recovery. “Versed ‘puts out the fire’ and lets the brain recover on its own time, usually within 48 to 72 hours,” explains Jeffrey Perlman, MD, Chief of Newborn Medicine at NYP/Komansky Center and Professor of Pediatrics at Weill Cornell Medical College. “If we induce cooling but we don’t sedate the infant, we may lose the protective effect of the cooling.”



Reducing a newborn’s body temperature to between 92.3° and 94.1° F within six hours of birth can decrease seizure risk.

In addition, Dr. Perlman’s group — which includes Eralyn Kasdorf, MD, Assistant Attending Physician and Assistant Professor of Pediatrics — uses high-dose prophylactic phenobarbital at the initiation of cooling to reduce seizure risk. Their observations cannot be confirmed through randomized clinical trials, however, because these studies would require too many subjects and take years to complete. So Dr. Perlman and his colleagues — including Susan J. Vannucci, PhD, Research Professor of Neuroscience in Pediatrics — have gone back to animal models of hypoxia-ischemia to evaluate their observations in an investigational setting. They’re already finding that high-dose phenobarbital appears to enhance the protective effect of cooling in the laboratory model.

Another drug to be evaluated for use with neonatal hypothermia is cromolyn, which is already used in inhaled form to prevent asthma symptoms. Cromolyn acts by stabilizing mast cells and blocking their migration, thereby reducing inflammation. In 2009, Dr. Vannucci and her colleagues reported that mast cells are early responders to hypoxia-ischemia in the neonatal rat brain. They also found that cromolyn prevented mast cell migration and reduced brain damage and neuronal loss, glial activation, and brain atrophy (*Stroke*. 2009;40:3107-3112). They concluded that

stabilization of mast cells with a medication such as cromolyn provides lasting protection. Mast cells may therefore represent a new target for therapeutic intervention to protect the fragile brains of newborns during the earliest days of their lives.

New Model Offers Hope for Evaluating Neonatal Antithrombotic Agents (continued from page 1)

several new models for this purpose (*Blood*. 2014;In press).

“We found that the mutated mice can serve as both a pharmacodynamic and functional response biomarker,” notes Dr. Diacovo. “These attributes are essential not only for expediting drug development, but also for designing clinical trials.” Moreover, they are aiding the testing of novel point-of-care devices that use minimal quantities of blood to assess the effectiveness of antithrombotic agents in neonates.

Pharmaceutical companies are already contacting NYP/Morgan Stanley Children’s about using the mouse model to assess their new anticlotting drugs for newborns. One promising new therapy is cangrelor, an inhibitor of the P2Y₁₂ receptor on platelets. Given intravenously, the drug is fast-acting but rapidly reversible. If indicated, therapy in a child can be stopped if excessive bleeding occurs, since withdrawing cangrelor halts its anticlotting effects almost immediately. This is in contrast to aspirin, whose effects may take days to resolve. In fact, it can take up to a week for a newborn to recover full platelet function.

“Aspirin can be very effective for preventing clots in most new-

borns, but it must be taken orally,” explains Dr. Diacovo. “We believe cangrelor could be particularly beneficial to prevent shunt thrombosis when used within the first 72 hours after neonatal cardiac surgery prior to starting aspirin therapy.” A clinical trial of cangrelor in children and adults in Europe is planned. If the results of testing in the mouse model and in the European study are promising, the drug could proceed to evaluation in a clinical trial at NYP/Morgan Stanley Children’s in one to two years.

The surgeons in the comprehensive Neonatal Cardiac Surgery program of the NewYork-Presbyterian Congenital Heart Center have been repairing congenital heart defects for decades. “Our center is already known for its expertise in neonatal cardiac surgery and has demonstrated clinical outcomes that exceed national benchmarks,” explains Richard A. Polin, MD, Chief of Neonatology/Perinatology at NYP/Morgan Stanley Children’s and William T. Speck, M.D. Professor of Pediatrics. “This antithrombotic research represents the next step in further improving the management of newborns requiring this complex level of care.”

Monitoring During Life's First Precious Moments

The most vulnerable point of a person's life are those first minutes of transition from a fetus to an infant. "That's why we call them 'The Golden Minutes,'" explains Richard A. Polin, MD, Chief of Neonatology/Perinatology at NewYork-Presbyterian/Morgan Stanley Children's Hospital and William T. Speck, M.D. Professor of Pediatrics at Columbia University College of Physicians and Surgeons.

A critical component of that transition is ensuring that a newborn is able to take its first breath — and if not, to initiate resuscitation efforts properly. Once a child is breathing, monitoring is still required to ensure that all continues to go well or to pinpoint potential problems as early as possible. At NYP/Morgan Stanley Children's, a number of initiatives are under way to enhance neonatal monitoring during the first minutes, hours, and days of a child's life.

For example, Tina Leone, MD, Assistant Attending Physician and Assistant Professor of Pediatrics, is developing ways to monitor newborns' vital signs during the first 10 to 15 minutes of life. Her goal is to use these data to create notifications for staff in the hospital's transitional nursery, enabling them to respond quickly when a problem is arising and resuscitation interventions may be needed. "During the first ten minutes of life, newborns are constantly changing," says Dr. Leone. "We are tracking their vital signs, and we will be able to provide feedback to the health-care team about interventions each child is likely to need." She's using the data to create a computer-driven training program that will simulate infants' vital signs and alert transitional nursery staff when early intervention is needed.

The concept of the transitional nursery was pioneered at NewYork-Presbyterian/Columbia in the 1960s. The four-bed unit near the labor and delivery rooms is staffed by neonatal intensive care specialists and provides care for infants awaiting transfer to the neonatal intensive care unit (NICU).

Similarly, with National Institutes of Health funding, Rakesh Sahni, MD, Attending Physician and Professor of Pediatrics, is collecting data from bedside monitors and ancillary monitoring devices on infants in all 62 beds of the NICU continuously to create a data repository and to develop predictive models that will serve as early indicators of neonatal infection and necrotizing



enterocolitis. Data are also being collected on oxygen exposure in extremely low birth weight infants during their entire course of stay in the NICU, with the goal of examining the effects of this therapy on pathology, including retinopathy of prematurity and chronic lung disease.

"Our goal is to identify newborns most at risk for having a life-threatening event and to use this information to improve their care and outcomes," explains Dr. Sahni. "This could become a powerful tool for predicting what might happen before it actually occurs, sparing infants from potential complications."

The NICUs of NewYork-Presbyterian

NewYork-Presbyterian/Morgan Stanley Children's Hospital, NewYork-Presbyterian Hospital/Phyllis and David Komansky Center for Children's Health, and NewYork-Presbyterian/Lower Manhattan Hospital have NICUs offering the latest specialized neonatal intensive care and staffed by specially trained nurses, nurse practitioners, and neonatologists. The NICUs at NYP/Morgan Stanley Children's and NYP/Komansky Center are also designated by the New York State Department of Health's Bureau of Women's Health as Regional Perinatal Centers.

When to Clamp the Cord: Before or After Neonatal Resuscitation? (continued from page 1)

hospital admission or death was higher among infants whose cords were clamped before they were able to take a spontaneous breath. That risk decreased by 20 percent for every 10-second delay in cord clamping after spontaneous respiration (*Pediatrics*. 2014;134:265-272).

Now neonatologists and ob/gyns are eager to know when to clamp the cords of infants who require resuscitation. The American College of Obstetrics and Gynecology wants to know, too. Because the placenta continues to perform gas exchange after childbirth, sick and preterm infants are likely to benefit most from the additional blood volume achieved by delaying cord clamping.

Dr. Perlman is initiating a study of larger preterm infants

(those born after 28 weeks) — with the consent of their parents, as well as the ob/gyns directing each delivery. In one group, cord clamping will be delayed for 30 to 60 seconds depending on whether the infant is making a respiratory effort. Infants in the second group will have the cord clamped at 30 seconds if they are not breathing, transferred to the resuscitation area, and then resuscitated. The researchers will compare neonatal outcomes.

"There is currently no guidance on cord clamping for infants who need resuscitation," says Dr. Perlman. "In terms of its correlation with experimental data and its implications for neonatal care, this could become an important contribution to the literature."

Focus on Neonatology

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