NEONATOLOGY TODAY

News and Information for BC/BE Neonatologists and Perinatologists

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Upcoming Medical Meetings
(See our website for additional meetings)

11th National Advanced Practice Neonatal Nurses Conference Sheraton
Apr. 23-26, 2014; Honolulu, HI USA
www.academyonline.org/APNNC

5th Phoenix Fetal Cardiology Symposium
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National Conference of Neonatal Nursing
Apr. 30-May 3, 2014; Las Vegas, NV USA
contact: ewhite@cforums.com

3rd International Symposium Perinatal and Neonatal Medicine 2014
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Annual Neonatal Advanced Practice Nursing Forum
May 28, 2014; Washington, DC USA
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Pitfalls During Neonatal Transport of Newborns with Hypoxic Ischemic Encephalopathy to Singapore General Hospital for Therapeutic Head Cooling

By Mary Grace S, Tan, MD; WB Poon, MD

Introduction

Hypoxic Ischemic Encephalopathy (HIE) remains a serious condition that causes significant mortality and long-term morbidity despite major advances in technology. It is characterized by clinical and laboratory evidence of acute or subacute brain injury due to asphyxia in the newborn period. This disease is prevalent in the newborn period. Preterm infants can also suffer from hypoxic ischemic encephalopathy, but the pathology and clinical manifestations are different. Most often, the condition is noted in infants who are term at birth. The symptoms of moderate-to-severe hypoxic-ischemic encephalopathy are almost always manifested at birth or within a few hours after birth. Often, the underlying cause remains unknown.

Extensive experimental data suggest that mild hypothermia (3°-4°C below baseline temperature) applied within a few hours (no later than 6 hours) of injury is neuroprotective. The neuroprotective mechanisms are not completely understood. Possible mechanisms include:

1. reduced metabolic rate and energy depletion;
2. decreased excitatory transmitter release; reduced alterations in ion flux;
3. reduced apoptosis due to hypoxic ischemic encephalopathy; and
4. reduced vascular permeability, edema, and disruptions of blood-brain barrier functions. The clinical efficacy of therapeutic hypothermia in neonates with moderate to severe hypoxic ischemic encephalopathy has been evaluated in 7 randomized controlled trials.[1-9]

The clinical efficacy of therapeutic hypothermia in neonates with moderate to severe hypoxic ischemic encephalopathy has been evaluated in seven randomized controlled trials.[1-9]

Accidental excessive hypothermia may result from exposure to a cold environment or from inadequate heat conservation. The body cannot produce enough heat to compensate for temperature below 33°C, thus it is an important cause of death in the newborn infant. This may occur at birth and during transportation.

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Complications of accidental hypothermia include: dysrhythmias, hypercarbia, azotemia, cold diuresis, electrolyte imbalance and coagulopathy, especially of the lungs and brain. Rewarming of the patient who has suffered from prolonged hypothermia presents with a greater problem. Thus, intense care is required to maintain the temperature during transportation.

Materials and Methods

In 2010, the Singapore General Hospital (SGH) Department of Neonatal and Developmental Medicine instituted a protocol for therapeutic hypothermia for neonates with moderate to severe HIE.

The typical sequence of events for initiating hypothermia therapy for outborn infants referred to our center is as follows:

1. Education to referring clinicians includes a recommendation to turn off the radiant warmer as soon as the diagnosis of acute perinatal moderate to severe HIE is considered (with temperature monitoring at least every 15 min) to maintain normothermia.
2. When an infant is born with suspected acute perinatal HIE, the referring clinician calls the neonatology consultant on call to arrange transfer.
3. Criteria for an acute perinatal hypoxic ischemic event and physical examination evidence of moderate or severe encephalopathy are discussed.
4. If the infant meets the criteria for therapeutic hypothermia, a recommendation is made to maintain either normothermia, or to continue passive cooling and closely monitor the rectal temperature (at least every 15 min, or continuously if possible). Aiming for a temperature of 34°-35°C. Active cooling in primary care hospitals before arrival of the transport team is discouraged. Neonatal transport was performed by the referring clinicians.

Case records from January, 2010 to December, 2012, of the 4 outborn hypoxic ischemic infants were retrieved. The demographic characteristics, clinical presentation, laboratory tests as well as clinical progress of these infants were collated and compiled. Neonatal transport procedures were reviewed and evaluated.

Of the four infants cooled before and during transport, no hospital recorded the temperature over the course of the entire transport. No cardiac arrhythmias other than sinus bradycardia were noted in any patient. When comparing patients who were overcooled to <34°C with those who maintained temperature in the 34 to 35°C range, there was a trend toward lower birth weight in those infants who were overcooled. There were no differences in admission vital signs or laboratory tests between the groups, although there was a trend toward lower platelet counts and higher blood sugar in overcooled infants as compared to appropriately cooled infants.

Discussion

Therapeutic hypothermia when applied within 6 hours of birth and maintained for 48-72 hours is a promising therapy for Hypoxic Ischemic Encephalopathy.[10,11] The timing of initiation of therapeutic hypothermia is critical, with optimum neuroprotection, if hypothermia is induced within 6 hours of an acute asphyxial insult.

Four Ex-Utero neonates with a diagnosis of hypoxic ischemic encephalopathy were transferred to Singapore General Hospital. See our criteria for head cooling in Table 3.

A database of patient information is maintained on all patients undergoing hypothermia therapy in our center. We reviewed clinical data of all outborn patients transferred to our

"Maintaining the temperature of hypoxic ischemic encephalopathic neonates during transfer is very important. Minimal handling to maintain therapeutic hypothermia must be the aim. Head Cooling is therapeutic; however, if it leads to accidental hypothermia, neonates are at high-risk of mortality and morbidity."

Table 1. Patient Demography

Patient	A	B	C	D
Gestational Age	37 weeks	39 weeks	35 weeks	39 weeks
Birth Weight	3306 gms	2895 gms	1850 gms	4630 gms
Nature of Amniotic Fluid	Clear	Thick meconium stained	Clear	Meconium stained
APGAR SCORE @ 1,5,10 and 15 mins	0,0,0 and 1	0,0,0 and 1	1,2 and 4,5	4,5,6 and 6
Antenatal Risk Factors	GBS(+),PE,GDM on Insulin	none	none	Anemia due to HbE Thalassemia, Polyhydramnios and fetal bradycardia
Thompson Score on Arrival to SGH	15	8	5	0
Time of Arrival at SGH	4 h of Life	12 h of Life	5 h of Life	3 h
Rectal Temperature on Arrival to SGH	34° C	31.8° C	31.5° C	35° C
BP on Arrival to SGH	68/43 (53)	78/55 (65)	55/44 (47) with dopamine	65/40 (42)
Diagnosis on Admission	HIE	HIE	HIE	Perinatal Depression
Method of Head Cooling	Selective head cooling	Selective head cooling	Selective head cooling	Not applicable

institution for therapeutic hypothermia from January 2010 to December 2012.

Out of the four outborn cases, three neonates met the criteria for head cooling; one neonate was not cooled, as the baby was vigorous on arrival to SGH. The majority of patients were passively cooled by the referring clinicians, overcooling to <34°C occurred in two patients, and there was no significant differences in laboratory values between overcooled and appropriately cooled infants except for the prolonged coagulation parameters among overcooled neonates. In fact, one out of two neonates that was overcooled had suffered from coagulopathy leading to intra-abdominal hemorrhage. This neonate also did not complete the hypothermia therapy because of shock and disseminated intravascular coagulation.

In this report, we highlight our efforts to educate health-care providers about the dangers of overcooling before and during transport and share suggestions for avoiding overcooling.

Educating referring clinicians about when and how to initiate therapeutic hypothermia is a cornerstone of a successful program. We recommend that in cases with suspected Hypoxic Ischemic Encephalothy, the radiant warmer should be turned off and the baby's temperature closely monitored during initial stabilization and neurological assessment to at least avoid hyperthermia. If the neurological examination is not consistent with moderate to severe encephalopathy, the baby can then be transitioned to routine thermal care. Asphyxiated, encephalopathic newborns are poor at thermoregulation and some will passively cool to a core temperature of less than 34°C range if left uncovered at room temperature.

As therapeutic hypothermia is increasingly used for neonates with hypoxic ischemic encephalopathy, whether and how to cool patients before arrival to a hypothermia center will be an important issue to resolve. Reports on feasibility and safety of cooling on transport indicate that initiation of hypothermia therapy at referring centers is possible, provided that ongoing education is in place for early transfer.[12]

With experience and education, referring and transport clinicians can induce and maintain hypothermia for asphyxiated neonates before and during transport. Neuroprotective temperatures are often achieved several hours sooner, and efforts to develop and evaluate protocols for safe transport of neonates undergoing induced hypothermia are warranted.

Conclusion

Maintaining the temperature of hypoxic ischemic encephalopathic neonates during

Table 2. Clinical Presentation and Progress of Affected Neonates

Patient	A	B	C
Complications of HIE	• Acute kidney injury • Hepatic dysfunction • Metabolic acidosis	• Acute renal impairment • Hepatic dysfunction • Metabolic acidosis	• Acute renal impairment • Metabolic acidosis
Laboratory investigations on admission	• CK15526 u/L • Trop - T 0.55 ug/L • NH4 69 umol/L • Lactate 20 mmol/L • Pyruvic Acid 24umol/L • ALP 192 u/L • ALT 69 u/L • AST 384 u/L • PT 44.1 secs • PTT 19 secs • Crea 99 umol/L • Platelet 109,000	• CK 387u/L • Trop - T 1.13 ug/L • NH4 60 umol/L • Lactate 3.1mmol/L • Pyruvic Acid 25umol/L • ALP 122 u/L • ALT 166 u/L • AST 97 u/L • PT 40.2 • PTT 82.9 • Crea 256 umol/L • Platelet 55,000	• CK 15,958 u/L • Trop - T 1.25 ug/L • NH4 67 umol/L • Lactate 23.1 mmol/L • Pyruvic Acid <12 umol/L • ALP 166 u/L • ALT 56 u/L • AST 241 u/L • PT >120,000 secs • PTT 103,000 secs • Crea 135 umol/L • Platelet 97,000
Blood gas on admission	• pH = 6.882 • pCO2 = 22.1 • pO2 = 289 • SaO2 = 100% • BE = -29 • HCO3 = 4.2	• pH = 7.202 • pCO2 = 21.5 • pO2 = 87 • SaO2 = 100% • BE = -20 • HCO3 = 8.4	• pH = 7.122 • pCO2 = 27.6 • pO2 = 218.9 • SaO2 = 98.9% • BE = -19 • HCO3 = 10.5
Time to achieve target temperature	4th hour of life	16th hour of life	Never achieved target temp as Selective head cooling aborted due to severe coagulopathy and hypotension at 17 h of life
Time to rewarm	4 hours	12 hours	Not applicable
Complications during cooling	• Seizures • Hyponatremia • Thrombocytopenia • Coagulopathy • Anemia	• Seizures • Hyponatremia • Thrombocytopenia • Coagulopathy • Anemia	• Hypotension • Hyponatremia • coagulopathy leading to adrenal and liver hematoma • Thrombocytopenia • Anemia
Time taken to achieve normal aEEG	Day 8 of Life	Day 7 of Life	Day 3 of Life
MRI findings	Areas of restricted diffusion in basal ganglia and thalami with increased lactate in basal ganglia and cerebral white matter. Small amounts of subdural hemorrhage and substantial cephalhematoma.	Findings consistent with HIE with evidence of signal changes in both globus pallidus and scattered areas of hyperintensity in both cortical and subcortical areas bilaterally.	Nil restricted diffusion, petechiae in bilateral occipital lobes.
Duration of hospital stay	37 days	29 days	17 days
Condition on Discharge	Complete tube feeding	Complete tube feeding	Oral feeding

Table 3: Inclusion Criteria

- Infants > 35 weeks gestation with one of the following
  - ➡ Apgar score <5 at 10 min after birth
  - ➡ Continued need for resuscitation, at 10 min after birth
  - ➡ Acidosis (cord pH/arterial pH within 60 min of birth <7.00)
  - ➡ Base deficit ≥ 12mmol/L(within 60 min of birth)
  - ➡ pH 7.01 – 7.15 and base deficit of between 10-11.9 mmol/L within 1st hour
- Moderate – Severe Hypoxic Ischemic Encephalopathy – based on HIE Scoring System by Thompson/Sarnat Score
- +/- Abnormal aEEG < 6 hours of life

transfer is very important. Minimal handling to maintain therapeutic hypothermia must be the aim. Cooling is therapeutic; however, if it leads to excessive hypothermia, neonates are at high risk of mortality and morbidity.

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Retinopathy of Prematurity Screening: Progress and Expansion with Telemedicine - an Interview with Darius M. Moshfeghi, MD

By Adrianne Resek, MA

"In the United States, people do not accept blind babies. There is a feeling that such a devastating handicap should be preventable," stated Darius Moshfeghi, MD of Stanford University. He is one of a handful of pediatric retina specialists that is actively trying to decrease the incidence of childhood blindness. For the last 8.5 years Dr. Moshfeghi has led the Stanford University Network for Diagnosis of Retinopathy of Prematurity (SUNDROP) telemedicine initiative, and he is involved in a number of universal newborn eye screening initiatives.

Retinopathy of Prematurity (ROP) is found in a small, but significant, number of premature babies, most of whom respond very well to treatment. An expansion in the screening guidelines to include a larger group of premature infants coincided with a decrease in the number of pediatric specialists performing the service. Because necessity is the mother of invention, Dr. Moshfeghi and his colleagues developed the SUNDROP remote telemedicine program that uses trained screeners at various locations to collect images of a newborn's eye using the RetCam wide-field digital imaging system (Clarity Medical Systems, Inc, Pleasanton, CA). "Images are collected at six remote locations by trained staff and then forwarded to me. I review the images for every infant that is screened, and if I see evidence of treatment-warranted disease, I either travel to the local site or have the baby transferred to my NICU to perform a dilated ophthalmoscopic exam of the patient before commencing treatment," states Moshfeghi.

While telemedicine is fairly broadly accepted today, when the SUNDROP program began many people had hesitations. To start with, binocular indirect biomicroscopy was the only officially accepted method for diagnosis of ROP. "There are several studies to investigate if multiple graders come to the same diagnosis after examining retinal images of premature babies, but we have never evaluated the sensitivity and specificity of a binocular indirect-ophthalmoscopy examination. It seems glaringly obvious to me that an image captured by a camera, which can be reviewed as many times and by as many experts as necessary, is a better means of diagnosis than a single individual viewing pathology and taking notes," states Moshfeghi. Diagnosis of ROP using wide-field digital imaging rather than indirect biomicroscopy has now been officially accepted, paving the way for expansion of SUNDROP and other telemedicine programs.

Ability to securely transfer images was another question when SUNDROP started. Not only has the concern of security dissolved, but new software has drastically increased the efficiency of image transfer. Synchronization software enables files to be automatically uploaded to a shared server once the camera is plugged into the network. The software also allows side-by-side image comparison and optional patient demographics. "I can efficiently evaluate the images right on the server, make my report and send it," comments Moshfeghi. "Not only is it much faster, it also eliminates user error. Babies go blind not because we lack effective treatment for ROP, but because we are not looking at them. This is due to a number of reasons including: technical difficulties, name changes or similar names, and multiple appointments. Anything that can be done to automate the screening process helps to eliminate human error."

"Because necessity is the mother of invention, Dr. Moshfeghi and his colleagues developed the SUNDROP remote telemedicine program that uses trained screeners at various locations to collect images of a newborn's eye using the RetCam wide-field digital imaging system (Clarity Medical Systems, Inc, Pleasanton, CA)."

SUNDROP has not disappointed. Five-year data from the program reported that 1022 eyes of 511 patients were screened, of which 15 had treatment-worthy pathology and underwent therapy. "In addition to the successful treatment of all patients identified as needing it, this telemedicine program had 100% sensitivity, 99.8% specificity, 93.8% positive predicative value, and 100% negative predictive value for detection of treatment-worthy ROP. In essence, one baby was recommended for referral and did not need treatment, and no babies that needed treatment were missed," reports Moshfeghi.

The SUNDROP team is now looking at ways that the program can expand. In addition to the possibility of increasing coverage to more remote locations, they are investigating universal eye screening for newborns. While there is no federal requirement for newborn screening, the American College of Medical Genetics convened a panel of experts in 2006 that recommended a uniform screening panel of 29 disorders including genetic, endocrine, and metabolic disorders or hearing loss. Of the 4 million newborns screened every year in the United States, 12,500, or 0.3%, are diagnosed with one of the core conditions.

Surprisingly, while premature babies meeting certain parameters are screened for retinopathy of prematurity, universal newborn eye screening is not among the recommendations in the guidelines. Universal newborn eye screening of over 16,000 babies in China has shown an incidence of congenital cataracts alone of 0.1%. Initial results of other universal newborn eye screening population studies show incidence of abnormal findings to be around 23%, including 20.96% with retinal hemorrhage and 2.28% with other pathologies including: subconjunctival hemorrhage, familial exudative vitreoretinopathy, abnormal fundus pigment, ocular dysplasia, lacrimal duct obstruction, retinal venous tortuosity, congenital cataract, retinoblastoma, optic nerve coloboma, and microphthalmos, each seen in a small number of patients.

Dr. Moshfeghi and colleagues are investigating the feasibility of universal eye screening in the United States with the Newborn Eye Screening Test (NEST) study. Eye screening is being offered in select hospitals to all newborns, with the promise of connecting them with the correct specialist should anything be found. "The current enrollment rate is around 25%, and we have screened close to 150 babies," states Moshfeghi. "We are finding significant pathology, nothing exotic to date, but pathology we can potentially intervene

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Most common adverse reactions associated with the use of SURFAXIN are endotracheal tube reflux, pallor, endotracheal tube obstruction, and need for dose interruption. During SURFAXIN administration, if bradycardia, oxygen desaturation, endotracheal tube reflux, or airway obstruction occurs, administration should be interrupted and the infant's clinical condition assessed and stabilized. Overall the incidence of administration-related adverse events did not appear to be associated with an increased incidence of serious complications or mortality relative to the comparator surfactants.

SURFAXIN is not indicated for use in acute respiratory distress syndrome (ARDS).

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INDICATIONS AND USAGE

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CONTRAINDICATIONS

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WARNINGS AND PRECAUTIONS

Acute Changes in Lung Compliance

Administration of exogenous surfactants, including SURFAXIN, can rapidly affect lung compliance and oxygenation. SURFAXIN should be administered only by clinicians trained and experienced in the resuscitation, intubation, stabilization, and ventilatory management of premature infants in a clinical setting with the capacity to care for critically ill neonates. Infants receiving SURFAXIN should receive frequent clinical assessments so that oxygen and ventilatory support can be modified to respond to changes in respiratory status.

Administration-Related Adverse Reactions

Frequently occurring adverse reactions related to the administration of SURFAXIN include bradycardia, oxygen desaturation, reflux of drug into the endotracheal tube (ETT), and airway/ETT obstruction.

Increased Serious Adverse Reactions in Adults with Acute Respiratory Distress Syndrome (ARDS)

Adults with ARDS who received lucinactant via segmental bronchoscopic lavage had an increased incidence of death, multi-organ failure, sepsis, anoxic encephalopathy, renal failure, hypoxia, pneumothorax, hypotension, and pulmonary embolism. SURFAXIN is not indicated for use in ARDS.

Clinical Trials Experience

The efficacy and safety of SURFAXIN for the prevention of RDS in premature infants was demonstrated in a single randomized, double-blind, multicenter, active-controlled, multi-dose study involving 1294 premature infants (Study 1). Infants weighed between 600 g and 1250 g at birth and were 32 weeks or less in gestational age. Infants were randomized to received 1 of 3 surfactants, SURFAXIN (N = 524), colfosceril palmitate (N = 506), or beractant (N = 258). Co-primary endpoints were the incidence of RDS (defined as having a chest x-ray consistent with RDS and an $FiO_2 \geq 0.30$) at 24 hours and RDS-related mortality at 14 days. The primary comparison of interest was between SURFAXIN and colfosceril palmitate with the intent of demonstrating superiority. Beractant served as an additional active comparator. Compared to colfosceril palmitate, SURFAXIN demonstrated a statistically significant improvement in both RDS at 24 hours and RDS-related mortality through Day 14. A second multicenter, double-blind, active-controlled study involving 252 premature infants was also conducted to support the safety of SURFAXIN (Study 2). Infants weighed between 600 g and 1250 g and were less than 29 weeks in gestational age. Infants received 1 of 2 surfactants, SURFAXIN (N = 119) or poractant alfa (N = 124).

The safety data described below reflect exposure to SURFAXIN administered intratracheally to infants at a dose of 5.8 mL per kg (up to 4 doses) in either 4 aliquots (Study 1) or 2 aliquots (Study 2) in 643 premature infants.

Comparator surfactants colfosceril palmitate and beractant were administered at the recommended doses (5.0 and 4.0 mL per kg, respectively) while the first dose of poractant alfa administered (2.2 mL per kg) was less than the recommended dose of 2.5 mL per kg. Any subsequent doses of poractant alfa were at the recommended 1.25 mL per kg dose.

Overall, the incidence of administration-related adverse reactions was higher in infants who received SURFAXIN compared to other surfactants (Table 1) and resulted in a greater proportion of infants treated with SURFAXIN who experienced administration-related oxygen desaturation and bradycardia. For Study 1, oxygen desaturation was reported in 17%, 9%, and 13% and bradycardia for 5%, 2%, and 3% of infants treated with SURFAXIN, colfosceril palmitate, and beractant, respectively. For Study 2, oxygen desaturation was reported in 8% and 2% and bradycardia in 3% and 2% of infants treated with SURFAXIN and poractant alfa, respectively. These adverse reactions did not appear to be associated with an increased incidence of serious complications or mortality relative to the comparator surfactants (Table 2).

Table 1. Administration-Related Adverse Reactions in SURFAXIN Controlled Clinical Studies[a]

	Study 1[b]			Study 2[c]	
	SURFAXIN (N = 524)	Colfosceril palmitate (N = 506)	Beractant (N = 258)	SURFAXIN (N = 119)	Poractant alfa (N = 124)
Total Doses Administered	994	1038	444	174	160
	Total Number of Events (Events per 100 Doses)				
ETT Reflux	183 (18)	161 (16)	67 (15)	47 (27)	31 (19)
Pallor	88 (9)	46 (4)	38 (9)	18 (10)	7 (4)
Dose Interruption	87 (9)	46 (4)	30 (7)	7 (4)	2 (1)
ETT Obstruction	55 (6)	21 (2)	19 (4)	27 (16)	1 (1)

[a] Table includes only infants who received study treatment.
[b] Study 1 doses were administered in 4 aliquots.
[c] Study 2 doses were administered in 2 aliquots.

Table 2. Common Serious Complications Associated with Prematurity and RDS in SURFAXIN Controlled Clinical Studies Through 36-Weeks Post-Conceptual Age (PCA)

	Study 1			Study 2	
	SURFAXIN (N = 527) %	Colfosceril palmitate (N = 509) %	Beractant (N = 258) %	SURFAXIN (N = 119) %	Poractant alfa (N = 124) %
Apnea	52	52	46	66	75
Intraventricular hemorrhage, all grades	52	57	54	39	38
-Grade 3/4	19	18	21	13	8
Periventricular leukomalacia	10	10	12	4	9
Acquired sepsis	44	44	44	45	52
Patent ductus arteriosus	37	35	37	43	44
Retinopathy of prematurity, all grades	27	26	25	32	31
-Grade 3/4	6	7	6	5	9
Necrotizing enterocolitis, all grades	17	17	19	13	15
-Grade 2/3	6	8	14	8	8
Pulmonary air leak through Day 7, all types	15	17	14	9	7
-Pulmonary interstitial emphysema	9	10	10	3	5
-Pneumothorax	3	4	2	4	1
Pulmonary hemorrhage	10	12	14	6	9

All-cause mortality through 36-weeks PCA was similar regardless of which exogenous surfactant was administered.

Adverse reactions reported in the controlled clinical studies through 36-weeks PCA occurring in at least 10% of infants were anemia, jaundice, metabolic acidosis, oxygen desaturation, hyperglycemia, pneumonia, hyponatremia, hypotension, respiratory acidosis, and bradycardia. These reactions occurred at rates similar to the comparator surfactants.

No assessments for immunogenicity to SURFAXIN were performed in these clinical studies.

Follow-up Evaluations

Twelve-month corrected-age follow-up of 1546 infants enrolled in the 2 controlled clinical studies demonstrated no significant differences in mortality or gross neurologic findings between infants treated with SURFAXIN and those treated with the comparator surfactants (colfosceril palmitate, beractant, or poractant alfa).

OVERDOSAGE

There have been no reports of overdose following the administration of SURFAXIN.

HOW SUPPLIED/STORAGE AND HANDLING

SURFAXIN (lucinactant) Intratracheal Suspension is supplied sterile in single-use, rubber-stoppered, clear glass vials containing 8.5 mL of white suspension (NDC 68628-500-31). One vial per carton.

Store SURFAXIN in a refrigerator at 2° to 8°C (36° to 46°F) and protect from light until ready for use. Do not freeze. Vials are for single use only. Discard any unused portion of SURFAXIN. Discard warmed vials of SURFAXIN if not used within 2 hours of warming.

To report SUSPECTED ADVERSE REACTIONS, contact Discovery Laboratories, Inc. at 1-877-SURFAXN (877-787-3296) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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with. That is exciting because if we find pathology, but we can't do anything about it, that decreases the value of the screening program. We are also separately conducting a validation study to figure out the most cost-efficient person who can provide effective screening." That program, the Global Universal Eye Screen Testing (GUEST) program is evaluating cohorts of individuals of various expertise at identifying eyes with pathology. At the simplest level, the primary outcome is to identify a cohort that can reliably identify the presence or absence of disease with a 98% agreement level. A key secondary outcome would be diagnosis agreement.

Telemedicine appears to be here to stay, and in the case of ROP at least, it is proving to be very effective. Increased access to preventative medicine is a win for everyone, and current and future studies will clarify the best practices for taking advantage of the latest technology.

Darius M. Moshfeghi, MD, is an Associate Professor of Ophthalmology at Stanford University, and Founder and Director of the SUNDROP Network.

He states that he has an equity interest in Visunex Medical Systems Co., LTD.

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JUNE MEDICAL MEETING FOCUS
Basic & Advanced Fetal Cardiology Symposium & Workshop
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http://fetalcardiacsymposium.com

A 2-day basic and advanced fetal cardiology symposium and workshop offering thorough and updated presentations on scanning the fetal heart and diagnosing and managing various common fetal congenital heart disease malformations. It will emphasize the basics of fetal cardiac scanning coupled with live case demonstrations and tips for diagnosing various anomalies. Presentations will focus on anomalies of the four-chamber and outflow-tracts views, reflecting the recent guidelines for screening for fetal heart disease.

The symposium will include sessions that focus on the latest updates in prenatal therapies and fetal cardiac and non-cardiac interventions, as well as new fetal imaging modalities. Attendees will have multiple opportunities to participate in hands-on workshops under the supervision of expert faculty in the field of fetal cardiology. There will also be opportunities to discuss interesting cases along with Q&A sessions.

Course Directors:
Sawsan M. Awad, MD, MSC; Karim Diab, MD, FACC, FASE

Course Co-Directors:
Ernerio T. Alboliras, MD, FAAP, FACC, FASE; John Bokowski, PhD, RDCS, FA; Xavier Pombar, DO; Mark Sklansky, MD

Invited National and International Faculty:
Lisa Hornberger, MD; Edgar Jaeggi, MD, FRCP(C); Anthony Johnson, DO; Carlos AC Pedra, MD, PhD; Simone Fontes Pedra, MD; Ra-id Abdulla, MD; Sawsan M. Awad, MD, MSC;John Bokowski, PhD, RDCS, FASE; Xavier Pombar, DO; Debra Selip, MD, FAAP; Michelle Rexilius, RDCS

Some of the Selected Topics Covered at the Meeting:
- Fetal Cardiac Screening: Basic Views and Red Flags
  Live Scanning: Step-by-Step Approach for Complete Fetal Echocardiography Study
- Practical Tips in Diagnosing Anomalies of the 4-Chamber View (TAPVR, AVC, Ebstein, ASD, VSD)
- Practical Tips in Diagnosing Anomalies of the 4-Chamber View (TA, MA/HLHS, DILV)
- Practical Tips in Diagnosing Anomalies of the Outflow Tracts (Truncus arteriosus/DORV/TOF-PA/Absent Pulmonary Valve)
- Practical Tips in Diagnosing Anomalies of the Outflow Tracts (TGA, AS, PS)
  Coarctation of the Aorta/ Interrupted Aortic Arch/ Vascular Rings
- Heterotaxy Syndrome and VisceroAtrial Situs Abnormalities
  Abnormalities of the Fetal Patent Ductus Arteriosus
  Borderline Common Cardiac Findings in the Fetus
- Cardiovascular Physiology: Pathophysiological Changes of CHD
- Fetal Arrhythmias: Diagnosis and Management
- How to Start a Fetal Cardiac Intervention Program
  Fetal Cardiac Intervention: Current and Future Directions
- Twin Twin Transfusion Syndrome: Cardiac Compromise and In Utero Treatment
- Fetal Intervention Ethics
  Fetal Cardiac Cases
- How to Evaluate Fetal Cardiac Function: Standard & New Modalities
- Recognition of Atrial Septal Restriction in Complex Congenital Heart Disease
- Family Counseling After Diagnosis of Fetal Abnormality
- And more....

Perinatal Probiotics: "Just to Have Some Dreaming, Dreaming is Free"

By Dennis T. Costakos, MD

While there is not enough evidence yet that administering probiotics to pregnant women will help reduce the chance of babies being born too early,[1] meta-analysis of 16 studies in probiotic-treated premature babies versus controls, suggests less Necrotizing Enterocolitis (NEC) and less all-cause mortality in probiotic treated patients.[2] While these 16 studies used multiple probiotics that have not cleared regulatory hurdles, and only a minority of the babies had birth weights below 1500 grams, and there were few exclusively breast fed babies in these 16 studies, the conclusions of meta-analysis was treat 33 babies to prevent one baby from developing NEC. NEC occurs in 6.5% of North American babies with 500 to 1500 grams birth weight and there is a 12 to 30% mortality and up to 50% morbidity if surgery is needed in these patients.

"While there is not enough evidence yet that administering probiotics to pregnant women will help reduce the chance of babies being born too early,[1] meta-analysis of 16 studies in probiotic-treated premature babies versus controls, suggests less necrotizing enterocolitis (NEC) and less all-cause mortality in probiotic treated patients.[2]"

In a recently published study, the Pro-Prems Trial, a prospective multicenter, double-blinded, placebo-controlled, randomized trial of 1099 infants from 10 centers born before 32 completed weeks gestation weighing <1500 grams 97%, exclusive breastfed, using bifidobacterium infantis, streptococcus thermophiles and bifidobacterium lactis containing 1 x 10^9 total organisms versus with placebo maltodextrin found that probiotics reduced NEC of Bell stage 2 or more (2.0% versus 4.4%). Relative risk 0.46, 95% confidence interval 0.23 to 0.93, P = .03; number needed to treat 43, 95% confidence interval 23 to 333.[4] The number to treat is very similar to the Cochran meta-analysis of 16 studies. Furthermore, since no adverse effects have been reported to date on probiotic intervention trials with premature babies, it is tempting to believe that very low birth weight babies are a group in which probiotic treatment independent of the breast milk advantage will become routine practice once we determine which is the most effective probiotic, combination of probiotics, when they should be started, what dosage should be used, and the duration of administration. In fact, in an ideal dream world, treatment of the expectant Moms will achieve the same results. To quote the rock group *Blondie*, "Just to have some dreaming, dreaming is free."

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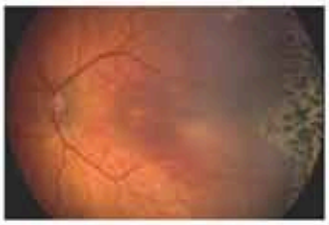

Image of Retinopathy of Prematurity

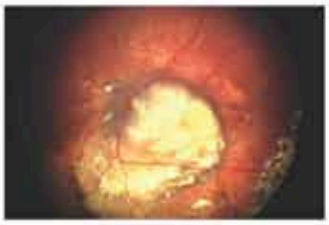

Image of Retinoblatoma

Image of Retinal Hemorrhages

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ESPGHAN = European Society of Paediatric Gastroenterology, Hepatology and Nutrition; HMF = human milk fortifier

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