TITLE: CARDIORESPIRATORY EVENTS IN PRETERM INFANTS IN NICU: EFFECTS OF SLEEP POSITION, STATE AND AGE
AUTHORS: Kelsee L Shepherd 1; Stephanie R Yiallourou 1,2; Alexsandria Odoi 1; Emma Yeomans 3; Rosemary SC Horne 1; Flora Y Wong 1,3
AFFILIATIONS: 1 The Ritchie Centre, Hudson Institute of Medical Research and Department of Paediatrics, Monash University, Melbourne, Australia. 2 Baker Heart and Diabetes Institute, Melbourne, Australia. 3 Monash Newborn, Monash Children’s Hospital, Melbourne, Australia.

CONTENT:
Preterm infants in NICU are often placed prone to improve respiratory function. Clinical guidelines recommend preterm infants are slept supine from 32 weeks of postmenstral age (PMA), regardless of gestational age (GA) at birth. However, respiratory dysfunction is related to GA and chronological age after birth rather than PMA. Respiratory function is also affected by the sleep state. Currently, the effects of the prone position on cardiorespiratory function in preterm infants in relation to age and sleep states remain unknown. We assessed the effects of position and sleep state on bradycardias, apnoeas and desaturations in preterm infants longitudinally, in relation to GA at birth and PMA.

Twenty-three extremely (24-28 weeks’ GA) and 33 very preterm (29-34 weeks’ GA) infants were studied weekly from birth until discharge, in prone and supine positions, and in quiet sleep (QS) and active sleep (AS). Cardiorespiratory events were defined as episodes of bradycardia (heart rate≤100 bpm), apnoea (pause in respiratory rate ≥10s), desaturation (oxygen saturation ≤80%) and percentages of time spent in each sleep states (QS% and AS%) were analysed. Frequency, duration and associated physiological data of the cardiorespiratory events, and %QS and %AS were analysed using a linear mixed model approach.

In extremely preterm, the prone position infants reduced the frequency of bradycardias and desaturations, and desaturation duration. The %QS was higher in prone compared to supine position. In contrast, in very preterm infants, prone positioning only reduced the frequency of desaturations. In the prone position, the very preterm infants had higher %QS and lower %AS compared to the supine position. The position-related effects in both groups of infants were not related to PMA or chronological age. QS reduced bradycardias and desaturations in both extremely and very preterm infants, but the effects are more marked in the very preterm infants. In the extremely preterm infants only, cardiorespiratory events reduced with increasing PMA rather than chronological age.

Prone-position-related benefits in cardiorespiratory function are dependent on GA but not PMA. Cardiorespiratory stability was improved by the prone position only in extremely preterm infants, with minimal effects in very preterm infants from PMA of 30 weeks onwards. The QS state has a more marked effect than the prone position in very preterm infants. This evidence should be considered in future recommendations for preterm infant positioning.

COI: None declared
ID: 97

TITLE: TIDAL BREATHING PARAMETERS IN INFANTS WITH TRANSIENT TACHYPNEA OF THE NEWBORN: IS STRUCTURED LIGHT PLETHYSMOGRAPHY FEASIBLE IN NICU?

AUTHORS: Evrim Alyamaç Dizdar 1; Davut Bozkaya 2; Fatma Nur Sarı 3; Esra Beşer 4; Cüneyt Tayman 5; Şerife Suna Oğuz 6

AFFILIATIONS: University of Health Sciences Ankara Dr zeikai Tahir Burak Women's Health, Health Application and Research Center, Ankara, Turkey

CONTENT:

Measurement of lung function helps in diagnosis, monitoring and treatment of respiratory diseases but conventional techniques such as spirometry are not possible in newborn babies. Structured Light Plethysmography (SLP) is a novel, non-contact, bedside respiratory assessment technique. It provides non-invasive tidal breathing measurement in patients difficult to cooperate such as newborns. Transient tachypnea of the newborn (TTN) is a self-limited disease commonly seen in late preterm infants born at gestational age between 34 and 37 weeks. Term and postterm babies are also at risk for TTN. The onset of TTN usually occurs within two hours after delivery. Tachypnea, nasal flaring, mild intercostal and subcostal retractions and expiratory grunting are the most prominent features.

In this study we aimed to measure tidal breathing parameters by SLP in infants with transient tachypnea of newborns (TTN) and compare with controls.

In this observational study, infants ≥34 gestational weeks with the diagnosis of TTN requiring NIV support and controls were recruited. The diagnosis of TTN was confirmed by clinical and laboratory data. Infants were excluded if they had major congenital anomalies, meconium aspiration, sepsis, perinatal asphyxia and RDS. Five minutes of tidal breathing was recorded using SLP (Thora-3Di, PneumaCare Ltd) in each infant. Various tidal breathing parameters including timing indices (RR, tI, tE, tTot, tI/tE and tI/tTot) flow-based parameters (tPTEF/tE, tPTIF/tI, IE50) and regional parameters (HTA, TAA, rCT) were obtained from SLP data.

Totally 87 infants underwent SLP measurements in the study. Evaluable recordings from 53 infants with TTN and 28 controls were analyzed after exclusions. Characteristics of the study infants were shown in Table 1. Among the timing indices RR was significantly higher in infants with TTN when compared with controls while tI, tE and tTot were significantly lower (p=0.017, p=0.024, p= 0.013 and p=0.017 respectively). Median IE50 levels in infants with TTN were significantly lower than controls (1.08 vs 1.29, p=0.015). Regional contribution of thorax, right and left hemithorax to total thoracoabdominal displacement in percentage were significantly higher in infants with TTN compared to controls (p=0.006, p=0.003 and p=0.013, respectively)

SLP is feasible to obtain measures of tidal breathing parameters even in newborns and it can give information about the respiratory parameters of infants with TTN.

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COI: None declared
ID: 225

TITLE: A PRETERM NEONATE-FOCUSED, NON-INVASIVE NEBULIZED SURFACTANT DELIVERY STRATEGY PROVIDES STABLE LUNG FUNCTION IMPROVEMENT IN multiple EXPERIMENTAL RESPIRATORY DISTRESS MODELS IN LINE WITH ITS LUNG DEPOSITION PERFORMANCE

AUTHORS: Dani C1, Bianco F2, Perez-de-Sa V3, Rey-Santano C4, Cunha-Goncalves D3, Mielgo V4, Schlun M5, Bucholski A5, Hetzer US, Nord A3, Linner R3, Bonelli S2, Lombardini M2, Pasini E2, Nutini M2, Murgia X6, Villetti G2, Civelli M2, Ricci F2, Minocchieri S7, Salomone F2

AFFILIATIONS: 1Department of Neurosciences, Psychology, Drug Research and Child Health, Careggi University Hospital of Florence, Florence, Italy.
2Department of Preclinical Pharmacology, R&D, Chiesi Farmaceutici S.p.A., Parma, Italy;
3Department of Cardiothoracic Anesthesia and Intensive Care, Lund University, Skåne University Hospital, Lund, Sweden.
4Animal Research Unit, Biocruces Health Research Institute, Barakaldo, Bizkaia, Spain.
5PARI Pharma GmbH, Starnberg, Germany.
6Department of Drug Delivery, Helmholtz Institute for Pharmaceutical Research Saarland, Saarbrücken, Germany.
7Division of Neonatology, Cantonal Hospital Winterthur, Winterthur, Switzerland.

CONTENT:

Non-invasive delivery of nebulized surfactant has been a neonatology long-pursued goal. A phase 2 dose ranging clinical trial (NCT03235986, Figure 1) is ongoing for investigating safety, tolerability, and efficacy of nebulized poractant alfa in premature infants ≥ 28 weeks by a customized eFlow Neos vibrating-membrane nebulizer system in preterm neonates with respiratory distress syndrome (RDS). Prior to human investigation, we characterized in vitro and in vivo this preterm neonate-tailored surfactant aerosolization treatment.

We investigated the aerosol output rate and particle size in vitro by laser-diffraction and Next Generation Impactor (NGI). Lung deposition was studied in vitro by breath-simulation experiments in a preterm upper-airway 3D model (PrINT-model) and in vivo by gamma scintigraphy in neonatal piglets managed with nasal continuous positive airway pressure (nCPAP) receiving technetium-labeled surfactant (200 mg/kg). Gas exchange, pulmonary mechanics, and reintubation rate were monitored in surfactant-depleted newborn piglets and adult rabbit RDS models managed with prongs-delivered nCPAP for either 3 or 72 hrs and treated with surfactant nebulization (dose investigated: 100, 200, 400, and 600 mg/kg). Animals treated with a surfactant-bolus (200 mg/kg) or nCPAP-only served as controls (n=9/group).

In vitro identified reproducible aerosol characteristics (volume median diameter of 3.0 μm and respirable fraction of 93.7%) for achieving an average of 17.9% surfactant lung delivery in clinical-like conditions on PrINT-model. Mean lung-deposition in newborn piglets validated these findings (15.9% of the nominal dose) in the in vivo setting. Nebulized surfactant treatments in both RDS models were well-tolerated and, according to the data in Table 1, associated both in acute (for dosages in the interval 200-600 mg/kg), at 3hrs, and at long term (for 400 mg/kg), at 72 hrs post-treatment, with significantly-improved arterial oxygen, lung function, and reintubation rate, comparable to bolus instillation recovery.

On the basis of the preclinical results three doses (200, 400 and 600 mg/kg) have been selected for the clinical investigation. The first part of the trial has been successfully concluded showing the safety of the procedure, the second part of the trial aimed at assessing efficacy is ongoing.
Figure 1. Phase 2 clinical trial design.
Table 1. Arterial partial pressure of oxygen versus fraction of inspired oxygen (PaO2/FIO2, mmHg), and dynamic compliance (ml/cmH2O/kg) values ± SEM at confirmation of respiratory distress before treatment and at the end of experiment (3 or 72 hrs according to each study design). Statistical analysis: 2-ways ANOVA with Tukey’s test. *p<0.05 comparing end of experiment value with respiratory distress value. #p<0.05 comparing surfactant treated groups vs. nCPAP group. Reintubation protocol has not been implemented for the 3 hours design. Consequently, values in the reintubation rate column for the 3 hrs studies are reported as not applicable (n.a.).

COI: SM, BA, HU are employees of Pari Pharma GmbH. ML, EP, MN, GV, FR, BF, RF, CC, BS, LM, PE, NM, PM, VG, CM, and SF are employees of Chiesi Pharmaceutici S.p.A.. MX, MS, and CD served as scientific consultants for this study.
ID: 312
TITLE: INTRA-TRACHEAL ADMINISTRATION OF BUDENOSIDE-SURFACTANT VERSUS SURFACTANT ONLY TO PREVENT BPD IN EXTREMELY PRETERM NEONATES: A RETROSPECTIVE CHART REVIEW
AUTHORS: Laura Moschino 1, Daniel Nardo 1, Matteo Stocchero 2, Luca Bonadies 1, Grazia Giunta 1, Sabrina Salvadori 1, Eugenio Baraldi 1
AFFILIATIONS: 1 Department of Women's and Children's Health, Neonatal Intensive Care Unit, University of Padua School of Medicine, Padua, Italy
2 Laboratory of Mass Spectrometry and Metabolomics, Department of Women's and Children’s Health, University of Padua School of Medicine, Padua, Italy

CONTENT:
Intra-tracheal (IT) administration of budesonide using surfactant as a vehicle has proved to be effective in reducing the risk of bronchopulmonary dysplasia (BPD) and the combined incidence of BPD or death at 36 weeks post-menstrual age (PMA) in very low birth weight (VLBW) infants with severe RDS. However, evidences on the outcomes and adverse effects of this therapy have not been widely explored.

The aims of this retrospective chart review analysis was to compare the effect of IT administration of surfactant/budesonide (SB) with that of surfactant only (S) in VLBW infants with severe RDS on the incidence of BPD, death and duration of mechanical ventilation (MV) before and after the introduction of SB strategy in our NICU.

IT SB strategy was introduced in our NICU in March 2018. Two cohorts of extremely preterm neonates (GA<28 GW, BW<1500 g), admitted at Padua’s NICU (Italy) and born in two consequent epochs (group S: 01/2017-02/2018, group SB: 03/2018-01/2019) were retrospectively compared. 72 neonates with RDS III-IV requiring respiratory support with FiO2≥0.3 within 12 hours of birth were enrolled. The SB group (n=35) received surfactant (200 mg/kg 1st dose; 100 mg/kg following doses) and budesonide (0.25 mg/kg). The S group (n=37) received surfactant only (200 mg/kg 1st dose; 100 mg/kg following doses). Medical team and management protocol of VLBW infants did not change between the two epochs. Data analysis was based on Fisher’s exact test, ANOVA, Kruskal-Wallis test, linear and logistic regression.

24 and 15 neonates from SB and S groups, respectively, were matched for GA, BW, number of SGA infants, and number of treatment doses to avoid possible confounding factors. Perinatal characteristics were similar at baseline in the two groups. The combined therapy of surfactant/budesonide did not affect the incidence of BPD, death, BPD or death at 36 weeks PMA, nor the risk of reintubation, extubation failure and severe IVH compared to surfactant therapy only (significance level 0.05). The incidence of adverse effects (hyperglycemia with 2 values>200 mg/dL in the first 3 days, insulin therapy, leucocytosis with WBC>30000/mm3 in the first 5 days, Candida infections in the first 14 days) did not differ between the two groups. A positive effect on hypotension (need for inotropes within the first 5 days) could be seen in the SB group (p=0.031), suggesting a systemic absorption of budesonide.

This retrospective chart review shows that early IT administration of budesonide with surfactant in VLBW neonates with severe RDS does not affect the incidence of BPD, death, and BPD or death at 36 weeks PMA, nor other respiratory outcomes, compared to treatment with surfactant only. Further RCTs studies with larger sample sizes are needed to investigate the benefits and adverse effects of early IT steroids.

COI: None declared
ID: 377

**TITLE:** LUNG ULTRASONOGRAPHY IN RESPIRATORY DISTRESS SYNDROME: AN EVALUATION OF DIFFERENT TYPES OF NATURAL SURFACTANTS

**AUTHORS:** Davut Bozkaya1
Evrim Alyamaç Dizdar1
Sabriye Korkut1
Burak Ceran1
Mihriban Alkan2
Şerife Suna Oğuz1

**AFFILIATIONS:**
1 Division of Neonatology, Zekai Thair Burak Women’s Health Training and Research Hospital, Faculty of Medicine, University of Health Sciences, Ankara, Turkey
2 Division of Radiological, Zekai Thair Burak Women’s Health Training and Research Hospital, Faculty of Medicine, University of Health Sciences, Ankara, Turkey

**CONTENT:**

Lung ultrasound (US) is a radiation free, easy and safe technique that helps in diagnosis, monitoring and management of many respiratory diseases in neonates. It provides assessment of lung aeration in preterm infants with RDS. Natural surfactants are the most commonly used surfactant preparations in the treatment of RDS. It is not clear whether significant differences exist among the available animal derived surfactant extracts. Some studies have compared natural surfactant preparations in terms of respiratory support, bronchopulmonary dysplasia (BPD) and mortality. However, effectiveness of different surfactants in RDS treatment have not been evaluated by lung ultrasound before. In this study we aimed to compare the lung ultrasound findings after two different natural surfactant administration as a parameter reflecting lung inflation.

In this prospective study, preterm infants with a gestational age less than 32 weeks who were diagnosed with RDS were randomly assigned to be administered either 100 mg/kg poractant alfa or 200 mg/kg beractant. Serial LUS scans were performed by an experienced neonatologist in a standardised manner before surfactant administration, 2 hours and 6 hours after administration of the surfactant. The LUS screening results were evaluated based on the systems developed by Brat and Raimondi et al.

Thirty-six infants were included in the poractant group and 37 were included in the beractant group. The demographic characteristics and pre-surfactant LUS scores were similar in both groups. In both groups, the scores were significantly decreased 2 hours and 6 hours after the application of the surfactant (2 hours; p = <0.001, 6 hours; p = <0.001). When the time points for each group were compared, the LUS scores were significantly lower in the poractant group than the beractant group.

When the LUS profiles were evaluated, the Type 1 RDS profile, before the administration of the surfactant, was observed in all infants except for one infant in the beractant group and two infants in the poractant group. At the end of the sixth hour, the number of infants with the Type 3 RDS profile (normal) was significantly higher in the poractant group (~65%) than the beractant group (22%).

Lung ultrasonography is useful for evaluating lung aeration after surfactant treatment in infants with RDS. We showed that preterm infants treated with poractant alfa showed faster recovery in the early period of the disease. However, further studies are needed to determine whether LUS might be effective in predicting the long-term consequences and efficacy of different types of surfactants in the treatment of RDS.
COI: • LUS, a non-invasive, easy-to-use and easy-to-interpret method
  • Lung ultrasonography is useful for evaluating lung aeration after surfactant treatment
  • Improvement in lung aeration results in a reduction in the requirement for respiratory and oxygen support
  • Proactant alfa corrected lung ventilation more quickly
ID: 396

TITLE: CHRONIC LUNG DISEASE OF PREMATURENESS SEVERITY SCALE: FACTOR SELECTION AND SCORING

AUTHORS: Robin Steinhorn 1; Mikko Hallman 2; Robert M. Ward 3; Ethan J. Schwartz 4; Magdalena Vanya 5; Ellen Janssen 4; Linda Han 6; Alexandra Mangili 7; Sujata P. Sarda 8

AFFILIATIONS: 1 Children’s National Health System, Washington, DC, USA; 2 University of Oulu and Oulu University Hospital, Oulu, Finland; 3 University of Utah School of Medicine, Salt Lake City, UT, USA; 4 ICON, Gaithersburg, MD, USA; 5 ICON, South San Francisco, CA, USA; 6 Shire, a Takeda company, Cambridge, MA, USA; 7 Shire, a Takeda company, Zug, Switzerland; 8 Shire, a Takeda company, Lexington, MA, USA

CONTENT:

Bronchopulmonary dysplasia (BPD; used interchangeably with chronic lung disease of prematurity [CLDP]) is a frequent comorbidity of extremely preterm infants.

We developed the chronic lung disease of prematurity severity scale (CLDPSS) for use in clinical trials with extremely preterm infants (<28 weeks gestational age), for the period between discharge to home from the neonatal intensive care unit (NICU) and 12 months corrected age (CA). Rounds 1 and 2 of a Delphi survey were previously conducted to identify factors in determining CLDP severity for inclusion in the CLDPSS. Here, we report Round 3 findings, including the importance of factors for determining CLDP.

In Round 2, clinicians had rated the importance of respiratory-related factors used to evaluate the severity of CLDP, from 0 (not at all important) to 10 (very important) for the period between discharge home from the NICU and 12 months CA. Clinicians also ranked the relative importance of these factors in determining severity. Thirteen factors were considered (Table). In Round 3 of the online survey utilizing Delphi methodology, clinicians were presented with aggregate results from Round 2 and were allowed to revise their previously provided responses to reach consensus. The relative importance and weighting of factors were explored through a set of 16 single-profile tasks (i.e., hypothetical patient profiles with varying CLDP severity levels).

The Round 3 survey was completed by 88 clinicians experienced in treating prematurity-related lung diseases such as CLDP (pediatric pulmonologists, n=50; pediatricians, n=19; neonatologists, n=19). Participants resided in 11 countries across North America, Europe, Asia, and South America. Findings from Round 3 indicated that the 4 most important factors in determining the severity of CLDP were home mechanical ventilation (mean absolute importance rating = 8.89), supplemental oxygen ≥ 2 L/min (8.49), re-hospitalizations (7.65), and supplemental oxygen < 2 L/min (7.56). The same 4 factors were also ranked most important relative to the others. According to single-profile tasks, supplemental oxygen had the largest influence on the predicted probability that a hypothetical patient profile would be classified as asymptomatic/minimal, mild, moderate or severe lung disease.

The four most important factors for clinicians in assessing CLDP severity during infancy were home mechanical ventilation, supplemental oxygen ≥ 2 L/min, respiratory-related re-hospitalizations, and supplemental oxygen < 2 L/min. Single-profile tasks highlighted the importance of oxygen-related factors. The current phase of CLDPSS development (clinician feedback) is complete. Refinement of the CLDPSS using patient data is planned.

IMAGES:
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Table. Factors Considered in the Delphi Survey
COI: This study was funded by Shire, a Takeda company. R. Steinhorn, M. Hallman and R. M. Ward, and were paid consultants to Takeda in connection with this study. E.J. Schwartz, M. Vanya and E. Janssen are, or were, employees of ICON and performed contracted research for Takeda in connection with this study. L. Han, A. Mangili and S.P. Sarda are employees of Shire, a Takeda company, and own stock/stock options in Takeda. The authors thank Rosalind Bonomally, MSc, employee of Excel Scientific Solutions, who provided medical writing assistance funded by Shire, a Takeda company.
ID: 441

TITLE: SUCCESS RATE OF NEONATAL INTUBATION WITH TWO DIFFERENT PREMEDICATION STRATEGIES

AUTHORS: Ellen H.M. de Kort 1,2; Irwin K.M. Reiss 2; Sinno H.P. Simons 2; Peter Andriessen 1

AFFILIATIONS: 1 Division of Neonatology, Department of Pediatrics, Máxima Medical Center, Veldhoven, the Netherlands
2 Division of Neonatology, Department of Pediatrics, Erasmus UMC – Sophia Children’s Hospital, Rotterdam, the Netherlands

CONTENT:

Awake intubation in neonates is associated with severe adverse physiological events. Premedication can decrease these adverse events, and reduce the number of attempts and the time needed for successful intubation. Since 2001 consensus is reached that premedication should always be used for nonemergency endotracheal intubation in neonates. Almost twenty years later, the most effective and safe premedication strategy is still to be discovered. Aim of this study was to evaluate success rate and technical quality of intubation in two different premedication strategies.

Prospective observational cohort study in a level III neonatal intensive care unit during a 30 month period. Neonates < 32 weeks’ gestation who required endotracheal intubation were eligible for inclusion. Only the first intubation encounter per patient was included. Intubation was performed according to a standardized procedure. At first, the local premedication regimen consisted of a combination of atropine, fentanyl and rocuronium (AFR group). After 17 months, the standard regimen was changed to atropine and propofol (AP group). Patient characteristics, pre-intubation sedation level, quality of intubation, number of attempts for successful intubation, total procedure time, and level of experience of the intubator were prospectively collected for both premedication regimens.

Patient and procedure characteristics of the AFR and AP groups are presented in table 1. In the AFR group 65% of patients was successfully intubated at the first attempt compared to 58% in the AP group (p = 0.32). Time to successful intubation was 15.7 ± 7.4 minutes in the AFR group, compared to 10.8 ± 7.7 minutes in the AP group (p < 0.001). Insufficient pre-intubation sedation level occurred significantly more often in the AP group than the AFR group (12 versus 0%, p = 0.03) and patients in the AP group significantly more often needed extra medication after the first attempt failed compared to the AFR group (48 vs 16%, p = 0.03). Quality of intubation was inadequate in 6% of patients in the AFR group and 8% of patients in the AP group respectively. This difference was not statistically significant (p = 1.0).

Success rates and quality of intubation were comparable between both premedication strategies. The total procedure time was significantly longer in the AFR group, due to our administration protocol taking into account the slower speed of onset of fentanyl. As longer procedure times may lead to adverse events, fast acting agents may be more appropriate. Further research into the efficacy as well as the safety of different strategies is needed.

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COI: None declared
ID: 755
TITLE: EVALUATION OF THE EFFECTS OF NEW BPD CLASSIFICATION BASED ON RESPIRATORY SUPPORT ON INCIDENCE OF BRONCHO PULMONARY DYSPLASIA
AUTHORS: Mehmet Buyuktiryaki1, Tuğba Alarcon-Martinez1, Bengu Karacaglar1, Gulsum Kadioglu Simsek1, Fuat Emre Canpolat, Cuneyt Tayman, H. Gozde Kanmaz Kutman
AFFILIATIONS: 1Division of Neonatology, Health Sciences University, Zekai Tahir Burak Women’s Health Education and Research Hospital, Ankara, Turkey.

CONTENT:

Bronchopulmonary dysplasia (BPD) is one of the most common respiratory morbidities of preterm newborns. The utility of commonly used BPD definitions are still controversial. Therefore, herein, we evaluate the effects of two different BPD classification: i) based on the National Institute of Child Health and Human Development (NICHD) and ii) based on requirement of respiratory support.

We assessed retrospectively the medical records of all preterm infants who were born at 250/7 to 296/7 weeks between 2013 and 2017. Based on recent BPD definition, patients were categorized according to the respiratory support provided at postnatal 36 weeks and independently from the required oxygen concentration. Newborns treated with low flow nasal cannula and newborns supported with high flow nasal cannula or any other non-invasive respiratory support were classified as mild BPD and moderate BPD, respectively. Patients under invasive mechanical respiratory support were classified as severe BPD.

Data analysis of 757 newborns revealed a mean gestational age of 28.1±1.5 weeks and a mean birth weight of 1024±241 g. According to NICHD and recent definitions, patients were evaluated and classified into mild BPD (%31.2-%0, respectively, p<0.001), moderate BPD (%9.2-%1.3, respectively, p<0.001) and severe BPD (%4.1-%1.2, respectively, p<0.001) (Table).

The evaluation of chronic lung disease in newborns with the recent BPD definition demonstrates a lower incidence of mild-moderate and severe bronchopulmonary dysplasia compared to previous NICHD classification. Further studies are needed for more sensitive and valid clinical classification to determine long-term outcomes, treatment and complications of BPD.

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BPD weight ratings according to NICHD and new classification

COI: None declared.
ID: 820
TITLE: A COHORT COMPARISON OF LESS INVASIVE SURFACTANT ADMINISTRATION IN A RESOURCE RESTRICTED INSTITUTION
AUTHORS: Lizelle Van Wyk 1; Johan Smith 2; Pierre Goussard ; Netta (IJ) van Zyl 4
AFFILIATIONS: 1,2,4: Division Neonatology, Dept. Paediatrics & Child Health, University of Stellenbosch, South Africa
3 Paediatric Pulmonology, Dept. Paediatrics & Child Health, University of Stellenbosch, South Africa

CONTENT:

Surfactant replacement therapy is the standard of care for neonatal respiratory distress syndrome. Survival has been shown to improve with CPAP and InSuRE in ELBW infants at Tygerberg Hospital, South Africa; a resource-restricted tertiary level public hospital with limited ventilation facilities. At Tygerberg Hospital, the ELBW birth and mortality rate are 60.2 and 83.3 per 1000 live births, respectively. All ELBW infants are supported with CPAP and less invasive SRT, if required. Recently, InSuRE has been replaced by LISA and surfactant supply by the Department of Health, South Africa, has changed from Curosurf to Survanta. The effect of these changes on neonatal outcomes are unknown.

Methods: A retrospective, medical record, comparative analysis was performed. A historical cohort of InSuRe administration, utilizing Curosurf (June 2007- May 2009), was compared to a contemporary cohort of LISA administration, utilizing Survanta (June 2015- May 2016), in ELBW infants with RDS at Tygerberg Children’s Hospital. Respiratory data were collected and infants underwent neurodevelopmental assessment at 1 year of age. Short-term (CPAP failure and/ or death prior to 72 hours of life) and long-term (death and/ or abnormal neurodevelopmental outcome at 1 year of age) composite outcomes were compared between the cohorts.

31.7% (97/306) and 43.8% (111/253) of ELBW infants received surfactant replacement in the historic and cohort groups, respectively, with an overall survival of 62.5% to discharge. The contemporary cohort received less doses of surfactant (1 vs 1.34, p=0.0004) but at an earlier age (3.2 vs 5.6 hrs, p=0.0001). There were no differences in CPAP failure, death prior to 72 hours of life, all-cause mortality or neurodevelopmental outcomes between the groups. Neither short-term nor long-term composite outcomes were affected by the method/surfactant combination. Both cohorts had very low BPD rates (<2%). The NNT to prevent CPAP failure or early death was 30 with a 3.39% risk reduction. NNT to prevent all-cause mortality/ abnormal neurodevelopmental outcome was 18.1 with a risk reduction of 5.53.

SRT increased between the two cohort eras with smaller and younger ELBW infants receiving minimally-invasive SRT with persisting low incidence of complications. Neither short-term nor long-term complications were accounted for by the combined method/ type of surfactant of SRT. Less invasive SRT methods, InSuRE and LISA, combined with CPAP, in ELBW infants is an effective management strategy in a resource-restricted environment.

COI: None declared
ID: 821

**TITLE:** NUTRITIONAL STATUS OF BABIES WHO DEVELOP BRONCHOPULMONARY DYSPLASIA: HOW CAN WE DO BETTER

**AUTHORS:** Irnthu Premadeva 1; Marika Lasokova 2; Amy Carmichael 3; Sateeshkumar Somisetty 3; Claudia Chetcuti-Ganado

**AFFILIATIONS:** Luton and Dunstable University Hospital

**CONTENT:**

Lung injury during fetal development has poor potential for recovery, making very preterm infants vulnerable to bronchopulmonary dysplasia (BPD). Undernutrition in their first few weeks of life impairs the canalicular-saccular stage of lung development and alters developmental programming through epigenetic modifications. The accumulation of calorie deficit is most prominent in the very low (VLBW) and extremely low birth weight (ELBW) babies and further perpetuates lung injury. The ESPGHAN recommendations provide guidance as to the target ranges of nutritional intake for optimal growth in preterm babies. There is no evidence for whether reaching these targets prevents BPD development.

Retrospective data was collected on babies born at a tertiary centre between 2014 and 2016 with a birthweight of less than 1.5Kg. Babies were excluded if they were transferred out or died before day 28 of life. The babies with a discharge diagnosis of BPD, defined as oxygen requirement or respiratory support at 36 weeks corrected gestation, were compared to those who did not. The ESPGHAN recommendations were used as the target range. We developed a nutritional calculator and the daily intake of fat, protein, carbohydrate and non-nitrogenous calories were obtained. The weight gain at day 28 was also compared between the two groups. Each baby’s background risk factors for developing BPD was collected as a surrogate marker of additional stresses that may increase calorie requirements.

A total of 28 babies were included in the analysis with n=14 in each group. The mean gestation and birth weight in the BPD and control groups were 27+4 and 1017g and 28+6 and 1018g respectively. Babies in both groups received similar protein and carbohydrate calories in the first 28 days. The protein intake for both groups was below the recommended range throughout the study period. A consistent lower intake of fat was noted in the BPD group which contributed to the overall lower non-nitrogenous calorie intake in this group. Higher rates of sepsis, blood transfusions, PDA requiring treatment, chorioamnionitis and longer days on mechanical ventilation were observed in the BPD group. Both groups had the same mean weight gain on day 28 of life. The control group received a higher volume of feed over the 28 days, maximally reaching 170.7ml/kg/day, versus 153.3ml/kg/day in the BPD group.

Optimisation of early postnatal nutrition as a strategy for reducing BPD rates in VLBW and ELBW babies, should take into consideration factors which increase metabolic demand. A lower fat intake creates a cumulative calorie deficit which is likely to contribute to lung injury. Weight gain is not a reliable marker of adequate nutritional intake. We recommend routine monitoring of fat, protein and carbohydrate intake as part of intensive care.

**IMAGES:**

[Link to image](https://www.eiseverywhere.com/eselectv3/v3/events/351149/submission/files/download?fileID=6e27eb5a9fd3fa3373b282f14ac8773-MjAxOS0wNSM1Y2UyNyY2YyYmQ1)

**COI:** None Declared
ID: 867
TITLE: GASTROINTESTINAL EFFECTS OF AN INHALED PDE4 INHIBITOR IN VENTILATED PRETERM LAMBS EXPOSED TO CHORIOAMNIONITIS
AUTHORS: Charlotte Van Gorp 1, Barbara Ottensmeier 2, Kimberly Massey 1, Tim Wolfs 1, Boris W. Kramer 1, Steffen Kunzmann 2, 3, Matthias C. Hütten 1, 2
AFFILIATIONS: 1 Neonatology, Department of Pediatrics, Maastricht University Medical Center, Maastricht, The Netherlands
2 Neonatology, University Children’s Hospital, University of Wuerzburg, Wuerzburg, Germany
3 Neonatology, Department of Pediatrics, Bürgerhospital and Clementine Children’s Hospital, Frankfurt, Germany

CONTENT:
Bronchopulmonary dysplasia (BPD) remains a therapeutic challenge in neonatology. New substances like phosphodiesterase (PDE) inhibitors, which have successfully been tested in clinical trials of pulmonary diseases of adulthood, have potential therapeutic benefits for BPD. However, when given enterally, adverse effects mainly in the gastrointestinal tract limit the clinical use. Inhalation might therefore be the preferable way of administration. We tested an inhalable PDE4 inhibitor in a triple hit lamb model of prematurity, Ureaplasma parvum-induced chorioamnionitis and mechanical ventilation. We hypothesized that inhaled PDE4 treatment would not induce gastrointestinal inflammation.

21 preterm lambs were in utero exposed for 7 days to Ureaplasma parvum chorioamnionitis, and surgically delivered preterm at 129d (term 150d). 16 animals were subsequently intubated, ventilated for 24 hours and received a nebulized PDE4 inhibitor twice in a higher dose (10 µg/kg, “IPDE10”), a lower dose (1 µg/kg, “IPDE1”), or no treatment (“Control”). Five lambs were sacrificed immediately after birth (“NOVENT”). Paraffin-embedded ileum sections were stained for CD3 and MPO and positive cells were counted in 5 random high power fields. PCR for mRNA of inflammatory cytokines was performed on homogenates of deep frozen ileum samples.

Histological evaluation of the ileum of PDE-inhibitor treated animals showed no significant increase of CD3 positive and MPO positive cells when compared to ventilated and unventilated controls. Inflammatory cytokine mRNA levels of IL-1, IL-6, IL-8 and TNF alpha showed a distinct pattern of inflammation in the high-dose group.

Our first analysis reveal dose-dependent, potentially adverse effects of inhaled PDE4 inhibitor on the gut of ventilated preterm lambs exposed to chorioamnionitis. Further analysis is performed to correlate pulmonary and intestinal effects.

COI: This study was supported by a grant from Deutsche Forschungsgemeinschaft (DFG-KU1403/6-1). No other potential conflicts of interest to declare.
ID: 893

TITLE: COMPOSITIONAL CHANGES ASSOCIATED WITH THE IMPROVEMENT OF PULMONARY SURFACTANT PERFORMANCE UNDER WHOLE BODY HYPOThERMIA

AUTHORS: Chiara Autilio 1; Mercedes Echaide 1; Shivani Shankar-Aguilera 2; Silvia Foligno 2; Jesus Perez-Gil 1; Daniele De Luca 2

AFFILIATIONS: 1 Department of Biochemistry and Molecular Biology, Faculty of Biology and Research Institute Hospital 12 de Octubre, Complutense University, Madrid, Spain
2 Division of Pediatrics and Neonatal Critical Care, South Paris University Hospitals, APHP, and South Paris-Saclay University, Paris, France

CONTENT:

WBH (33.5°C) is an effective treatment for neonates with encephalopathy due to perinatal asphyxia, but has also several biological effects on neonatal lungs. For instance, we previously demonstrated a reduction in both lung inflammation and secretory phospholipase A2 activity in cooled neonates [1,2]. At the same time, we observed a temperature dependent improvement of pulmonary surfactant (PS) activity after 72h of WBH [3]. Since in vivo DPPC turn-over does not seem to vary during cooling [4], we investigated whether other compositional changes could explain this temperature- and time-dependent improvement of PS performance.

5 asphyxiated neonates without lung disease received nonbronchoscopic BAL before and after 72h of WBH [5]. Large aggregates (LA) of PS were precipitated (1h at 40,000 g) to test: 1) the amount of surfactant proteins SP-B and SP-C by western blot analysis, and 2) the percentage of lipid classes and subclasses by lipidomic analysis (UPLC-TOF). Total proteins (TP) and phosphatidylcholine (PC) amount were also measured by colorimetric methods.

No changes in TP and total PC were obtained. SP-B amount did not vary, but a significant decrease in SP-C content was observed after 72h of WBH [pre=72(70-74)%; 72h=0(0-18)%, p=0.027]. At this time point, the percentage of some unsaturated PC (unPC) species significantly decreased, promoting a simultaneous increase in DPPC proportion [unPC(34:2): pre=12.1(11.3-12.6)%; 72h=9.7(8.5-10.8)%; p=0.039], [unPC(34:3): pre=2.4(2.0-2.7)%; 72h=0.85(0.6-1.0)%; p=0.018], [DPPC: pre=41.8(39-45)%; 72h=45.8(45-46)%; p=0.051].

The boost in PS activity under WBH may be partially explained by a better exclusion of less active lipid species from large surfactant membranes at 33.5°C, promoting a simultaneous increase in DPPC proportion.


COI: no conflict of interest
ID: 903

**TITLE:** POSTNATAL DEXAMETHASONE ACTS BY LIMITING MACROPHAGE MEDIATED INFLAMMATION AND UPREGULATING SURFACANT PROTEIN MRNA IN THE LUNG.

**AUTHORS:**
1. Jonathan Davis
2. Veena Kurup
1,2. Peter Noble
1,2. Siavash Ahmadi-Noorbakhsh
2,3. MJ Dahl
3. Kurt H Albertine
2. Amy Wooldridge
2,4. Paris Papagianis,
1,2. Jane Pillow

**AFFILIATIONS:**
1. Centre for Neonatal Research & Education, University of Western Australia, Perth;
2. Human Sciences, University of Western Australia, Perth;
3. Dept of Paediatrics, University of Utah, Salt Lake City, UT, USA,
4. School of Heath and Biomedical Sciences, RMIT University Melbourne

**CONTENT:**

The immunological and surfactant response of the ventilated preterm lung to postnatal glucocorticoids are described poorly. This study aimed to describe these aspects of early postnatal lung development in response to ventilation and early low-dose dexamethasone.

Ewes were delivered operatively at 129d after antenatal betamethasone (5.7mg, 48 and 24h prior). Lambs were intubated and received surfactant (poractant alpha; 100mg/kg), then volume-targeted ventilation (~6mL/kg) and graduated weaning of respiratory support as tolerated. Lambs were randomised to tapered IV saline (SAL, n=9) or dexamethasone (DEX, n=8; commencing 0.15 mg/kg) from ~2h age, and euthanised at 7d. Fetal controls (FC, n=5) were euthanised at 136d. Lung tissue was stained for macrophage (CD163), leucocyte (CD45) and smooth muscle (SMA). Cell number/field were averaged from 72 fields/lamb. Surfactant protein (SP) mRNA was measured using a Fluidigm assay. Cell counts and relative mRNA expression were compared using Mann–Whitney (SAL vs FC; DEX vs SAL) and reported as median (IQR).

Demographics are shown in Table 1. The number of CD163 and CD45 positive cells/field increased in SAL vs. FC (238 (115–411) vs. 2.3 (1.3–10.2); p=0.009 and 48(40–59) vs 0.3(0.6); p=0.06) respectively. Dexamethasone decreased the number of CD163 positive cells/field (44(34-115)) vs. SAL lambs (238 (145-411; p=0.003)) but did not alter CD45 cell counts. SMA expression (positive cells/field) increased in SAL (933(815–1032) vs FC (577(461-813); p=0.04) but was unchanged by dexamethasone. Dexamethasone increased relative gene expression of SP-A (DEX vs. SAL, 164(72–526) vs 27.3(14.7–45.5); p<0.005) and SP-C (DEX vs. SAL, 13.1(7.8–34.9) vs7.7(5.2–9.4); p <0.05). Similar but non-significant increases in gene expression of SP B (p=0.09) and SP-D (p=0.05) were observed.

Preterm lambs receiving contemporary lung protective ventilation have evidence of pulmonary inflammation at 7-days compared to gestation and antenatal exposure matched fetal controls. A tapered low-dose course of dexamethasone from soon after birth decreased pulmonary inflammation and increased gene expression of surfactant proteins. The anti-inflammatory effect of dexamethasone was restricted to macrophage mediated inflammation.
Table 1. Characteristics of the study population

**COI:** Unrestricted support: National Health and Medical Research Council (Australia) GNT1057759; 1057514, 1077691; Chiesi Farmaceutici S.p.A. (surfactant); F&P Healthcare (circuits), ICU Medical (monitoring lines).
ID: 924

**TITLE:** THE EFFECT OF RESPIRATORY MANAGEMENT VARIATIONS ON BRONCHOPULMONARY DYSPLASIA IN EXTREMELY PRETERM INFANTS

**AUTHORS:** Sunjuri Zhi Yu Sun 1; Charles Christoph Roehr 2; Arul Earnest 3; Kenneth Tan 4

**AFFILIATIONS:**
1 Department of Paediatrics, School of Clinical Sciences (SCS), Monash University, Melbourne, Australia
2 Department of Paediatrics, Medical Sciences Division, University of Oxford, Oxford, United Kingdom
3 Department of Public Health and Preventive Medicine, Monash University, Melbourne, Australia
4 Department of Paediatrics, School of Clinical Sciences (SCS), Monash University, Melbourne, Australia

**CONTENT:**

Recent comparisons between different national neonatal registries have shown variations in clinical outcomes such as survival and bronchopulmonary dysplasia (BPD). There is often greater inter-centre variability in terms of clinical practices and respiratory management strategies, which warrants further investigation of how these variations influence neonatal outcomes, in particular BPD. The aim of this study was to evaluate if different respiratory management styles exist between two neonatal units in differing healthcare systems and if variations in respiratory management strategies for extremely preterm infants have any effect on the risk of BPD outcome or mortality.

A retrospective cohort study was conducted for all extremely preterm infants admitted to Monash Newborn at the Monash Children’s Hospital (Melbourne, Australia) and the Oxford Newborn Care Unit at the John Radcliffe Hospital (Oxford, United Kingdom) over a period of three years, from 2015 to 2017 inclusive. Statistical analysis was performed using Stata/IC Version 14.0 for Mac (StataCorp LLC 2015: Texas, USA). To compare two independent population medians, the two-sample Wilcoxon rank-sum test was used and for categorical data, the chi-squared test was performed. Multiple logistic regression was performed to analyse the contribution of various determinants on the development of BPD. A total of 492 infants were included in the study – 310 from Oxford and 182 from Monash.

The overall incidence of BPD for extremely preterm infants was 62.20%. There was a significantly higher crude mortality rate at Oxford compared to Monash (6.59% at Monash vs. 16.45% at Oxford, p=0.002). There was no difference in terms of the combined outcome of BPD or mortality between study sites (70.88% at Monash vs. 76.45% at Oxford, p=0.172). Oxford had significantly higher rates of intubation at resuscitation, surfactant administration and use of nitric oxide. Monash used nasal CPAP and parental nutrition more frequently than Oxford. Independent risk predictors for the development of the combined outcome (BPD or mortality) included the use of nitric oxide (adjusted odds ratio 18.257, 95% CI 2.358-141.337, p=0.005), days on mechanical ventilation (adjusted OR 1.134, 95%CI 1.074-1.197, p=0.000) and days on high flow oxygen therapy (adjusted OR 1.017, 95% CI 1.002-1.034, p=0.029).

Bronchopulmonary dysplasia remains a significant cause of neonatal morbidity amongst extremely preterm infants. Despite significant differences in clinical practice, both units had similar rates of the composite outcome (BPD or mortality). Use of nitric oxide, days on mechanical ventilation and days on high flow oxygen were independent predictors of the primary outcome.

**COI:** None declared
ID: 956

TITLE: OBJECTIVE PHARMACODYNAMIC EVALUATION OF DOXAPRAM THERAPY IN PRETERM INFANTS

AUTHORS: Jarinda Poppe 1; Willem van Weteringen 2; Swantje Völler 3; Sten Willemsen 1,5; Tom Goos 1,4; Irwin Reiss 1; Sinno Simons 1

AFFILIATIONS: 1. Department of Paediatrics, division of Neonatology, Erasmus MC - Sophia Children’s Hospital, Rotterdam, The Netherlands
2. Department of Paediatric Surgery, Erasmus MC - Sophia Children’s Hospital, Rotterdam, The Netherlands
3. Division of Pharmacology, Leiden Academic Centre for Drug Research, Leiden, The Netherlands
4. Department of Biomechanical Engineering, Faculty of Mechanical Engineering, Delft University of Technology, Delft, The Netherlands
5. Department of Biostatistics, Erasmus MC, University Medical Centre Rotterdam, Rotterdam, The Netherlands

CONTENT:

Pharmacodynamic evaluation is very challenging in newborn infants. It is often based on subjective, intermittent human interpretation of clinical and physiological parameters. Continuously available physiological monitor data provide the exciting opportunity of continuous and objective drug evaluation. This concept is potentially very relevant for the evaluation of doxapram therapy, a respiratory stimulant to avoid mechanical ventilation and adverse outcomes of hypoxemia in preterm infants. The aim of the study was to evaluate the pharmacodynamics of doxapram therapy using continuously available physiological and ventilatory parameters.

Preterm infants admitted to a level III NICU centre who received doxapram therapy were eligible for inclusion. Stored physiological and ventilatory parameters were analysed. Additionally, the oxygen saturation (SpO2)/fraction of inspired oxygen (FiO2)-ratio and the area under the 89% SpO2 curve (duration x depth of SpO2 dips) were calculated. Trends (mean ± SD) of all parameters were visualized to evaluate the therapy effects. Logistic regression analyses were performed to predict therapy failure (intubation or death) or success per hour in the 2 days around therapy start.

The first episode of doxapram therapy was analysed in a total of 61 preterm infants with a median postmenstrual age at therapy start (PMA) of 28.7 weeks (Q1-Q3; 27.6-30.0). The success rate of doxapram therapy was 57%. In 11% of the patients therapy failed within 24 hours. The effects of doxapram were clearly present in the trends of the SpO2/FiO2-ratio and the Area under the SpO2 curve (Figure 1). Out of all parameters, the SpO2/FiO2-ratio showed to be the most indicative of therapy outcome. The predictive models in the 2 days around therapy start included therefore the SpO2/FiO2-ratio, corrected for the PMA. According to the relative quality of the models, therapy outcome can be predicted best at 10 hours after therapy start (AUC of 0.83). The SpO2/FiO2-ratio was inversely associated with therapy outcome (OR 0.30, CI 95% 0.13-0.64; p < 0.01).

The effects of doxapram can be clearly observed in the trends of the SpO2/FiO2-ratio and the Area under the SpO2 curve. The SpO2/FiO2-ratio at 10 hours after doxapram start is the most predictive of therapy failure or success. The use of continuous physiological data provides a new method for objective evaluation of neonatal therapy.

IMAGES:
https://www.eiseverywhere.com/eselectv3/v3/events/351149/submission/files/download?fileID=31ee06c61322bfc7b5bcbddd5bc9a49d-MjAxOS0wNSM1Y2UyNjY2MzDmxY2Qx

Figure 1. The trend in the SpO2/FiO2-ratio and the Area under the SpO2 curve from 7 days before until 14 days after therapy start.

COI: None declared
ID: 958

TITLE: CYTOKERATIN FRAGMENT 21-1 IS ASSOCIATED WITH MORTALITY AND LONG-TERM OXYGEN THERAPY IN NEONATES WITH CONGENITAL DIAPHRAGMATIC HERNIA.

AUTHORS: Florian Kipfmueller 1, Kartin Heindel 1, Stefan Holdenrieder 2, Peter Bartmann 1, Andreas Mueller 1

AFFILIATIONS: 1 Department of Neonatology and Pediatric Critical Care Medicine, Children's Hospital, University of Bonn, Germany
2 Department of Clinical Biochemistry and Laboratory Medicine, Bonn Medical Center, University of Bonn, Germany

CONTENT:

Lung hypoplasia is a major contributor to morbidity and mortality in neonates with congenital diaphragmatic hernia (CDH). Therefore, CDH newborns are at high risk for ventilator-induced lung-injury. The cytokeratin fragment 21-1 (C21-1) is part of the pulmonary cytoskeleton, providing cell stability and cell-to-cell communication. An increased detection of circulating C21-1 might be associated with poor outcome in CDH neonates. Aim of this study was to investigate the prognostic role of C21-1 in CDH neonates.

CDH neonates treated in our department 2014-2018 were eligible for prospective enrollment. C21-1 was measured from arterial blood using electroluminescence immunoassay at the age of 6, 12, 24, and 48 hours. The primary clinical endpoint was death or oxygen dependency at day 28 (BPD). C21-1 concentration was compared in CDH neonates with and without the clinical endpoint using Mann-Whitney-Test.

90 CDH neonates were prospectively enrolled, 40 met the primary endpoint death/BPD (death n=19; BPD n=21). Patients in the death/BPD group had significant lower lung volumes and higher proportion of intrathoracic liver herniation. C21-1 was significantly higher in the death/BPD group at 6 hours (p<0.001), 12 hours (p=0.005), 24 hours (p<0.001), and 48 hours (p90. percentile at least at one time met the clinical endpoint in 94.4% while this occurred in 31.9% of patients with C21-1 always 90. percentile) versus 13.9% (<90. percentile), respectively. A significant correlation of C21-1 with the highest oxygenation index and highest peak inspiratory pressure in the first 24 hours of life was observed.

High C21-1 levels were associated with increased incidence of death and BPD in CDH newborns and correlated well with the severity of respiratory failure. C21-1 could serve as a prognostic biomarker in high-risk neonates.

IMAGES:
https://www.eiseverywhere.com/eselectv3/v3/events/351149/submission/files/download?fileID=8432146be02aae941898ff101c236628-MjAxOS0wNSM1Y2UyNjY2ZDMyZy

Table: Baseline and outcome data

COI: None declared
ID: 966

TITLE: EFFECTS OF GLOBAL HYPOXIA-ISCHEMIA AND MESENCHYMAL STEM CELL TREATMENT ON PRETERM OVINE LUNGS

AUTHORS: Monique GM Willems 1; Daniele Panichi 2; Reint K Jellema 3; Daan RMG Ophelders 4; Maria Nikiforou 5; Nico Kloosterboer 6; Danilo AW Gavilanes 7; Steffen Kunzmann 8; Tammo Delhaas 9; Tim GAM Wolfs 10; Boris W Kramer 11.

AFFILIATIONS: 1 Department of Pediatrics; Department of BioMedical Engineering; School for Oncology and Developmental Biology, Maastricht University Medical Center, Maastricht, The Netherlands.
2 Department of Pediatrics; School of Oncology and Developmental Biology, Maastricht University Medical Center, Maastricht, The Netherlands.
3 Department of Pediatrics, "G. D'Annunzio" University, Chieti, CH, Italy
4 Department of Pediatrics; School of Mental Health and Neuroscience, Maastricht University, Maastricht, The Netherlands.
5 Department of Pediatrics; School of Mental Health and Neuroscience, Maastricht University, Maastricht, The Netherlands.
6 Department of Pediatrics; School of Mental Health and Neuroscience, Maastricht University, Maastricht, The Netherlands.
7 Department of Pediatrics; School of Mental Health and Neuroscience, Maastricht University, Maastricht, The Netherlands.
8 Department of Medical Engineering; School for Cardiovascular Diseases, Maastricht University, Maastricht, The Netherlands.
9 Department of Biomedical Engineering; School for Cardiovascular Diseases, Maastricht University, Maastricht, The Netherlands.
10 Department of Pediatrics; School of Oncology and Developmental Biology; Department of Biomedical Engineering; School for Cardiovascular Diseases, Maastricht University, Maastricht, The Netherlands.
11 Department of Pediatrics; School of Oncology and Developmental Biology, Maastricht University, Maastricht, The Netherlands.

CONTENT:

Perinatal asphyxia (PA) is a condition of impaired gas exchange during birth, leading to fetal hypoxia-ischemia (HI) and is associated with postnatal adverse outcomes such as hypoxic-ischemic encephalopathy (HIE) and necrotizing enterocolitis (NEC). Intravenous mesenchymal stem cells (MSC) administration showed therapeutic effects for HIE, but not in gut injury after HI in animal models. Few data are available about the effects of global HI on fetal lungs and the potential role of MSC cells. The aim of this study was to assess inflammatory and lung maturation effects after global HI and the potential role of intravenously delivered MSCs in an ovine model of global HI.

In a preclinical ovine model, 28 fetuses at gestational age of 106d were randomized in 4 arms in which either umbilical cord occlusion (UCO) or sham was performed for 25 min followed by intravenous administration of either MSC cells (2x10^6/kg) or saline. The fetuses were euthanized 7d after UCO or sham. Lungs were stained for CD3 and MPO as inflammatory markers for T lymphocytes and neutrophils/macrophages, respectively. Additionally, the mRNA levels of the following cytokines were assessed: IL-1, IL-6, IL-8, IL-10. To assess lung maturation, we measured surfactant protein (SP)-A, -B, -C, -D mRNA levels and SP-B concentrations.

Total number of MPO+ and CD3+ cells in lungs did not differ between HI and control group. IL-1, 6, 8 mRNA levels were not statistically different between the groups. IL-10 mRNA was 4 fold higher in HI-MSC group than in control (p<0.05). The surfactant protein mRNA levels (SP-B) were increased in UCO group with MSC treatment. SP-B protein concentrations were increased after UCO. The intravenous administration of MSC did not change the increase of SP-B protein after UCO.
Global HI in combination with intravenous MSC cells administration induced increases in surfactant protein B concentrations and mRNA levels in the absence of inflammatory changes. Additional experiments are needed to understand the effects of systemic MSC in HI on the fetal lung.

**COI:** None declared