ID: 69  
TITLE: NEBULIZED PORACTANT ALFA REDUCES THE RISK OF RESPIRATORY FAILURE AND REINTUBATION AT 72 HOURS IN SPONTANEOUSLY-BREATHING SURFACTANT-DEFICIENT NEWBORN PIGLETS.  
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 CONTENT:  
The short-term efficacy of nebulized poractant alfa has been studied in animal models showing an acute pulmonary improvement at 3 hours. However, the primary efficacy outcome in clinical trials aimed at investigating non-invasive surfactant administration techniques is the rate of failure as measured by the need for intubation and surfactant instillation in the first 72 hours of life. We have set up a long term (72 hours) respiratory distress syndrome (RDS) model in spontaneously-breathing surfactant-deficient newborn piglets to investigate the rate of respiratory failure of nebulized poractant alfa compared to standard InSurE (Intubation Surfactant Extubation) technique and nasal CPAP only.  
Eighteen spontaneously breathing newborn piglets (n=6/group), were submitted to bronchoalveolar lavages to induce surfactant-deficient RDS, and then were randomized to three nasal CPAP (nCPAP)-ventilated groups: 1) nebulized poractant alfa (400 mg/kg; dose chosen from previous 3-hour study for exemplary purpose only, not predictive yet of the most suitable dose for clinical use) via a customized eFlow Neos vibrating-membrane nebulizer system, 2) bolus administration using InSurE technique (200 mg/kg) or 3) nCPAP only. Pulmonary (gas exchange, lung mechanics) and hemodynamic (arterial blood pressure, heart rate) parameters were evaluated at 6-hour intervals for 72 hours. Lung and brain histological analyses were also performed.  
After bronchoalveolar lavages, newborn piglets developed RDS. During the 72 hours observation, both surfactant treatment groups significantly improved pulmonary outcomes compared to nCPAP only, without hemodynamic alteration. Moreover, differently from nCPAP group, in both surfactant treatment groups there were no cases of respiratory failure.  
In newborn piglets with RDS, the nebulization of 400 mg/kg of poractant alfa by means of a customized eFlow Neos nebulizer system showed to be safe and effective in reducing the risk of respiratory failure in the first 72 hours after treatment. This finding needs to be verified in a randomized control trial in spontaneously-breathing newborn infants.  
Supported by: Chiesi-Farmaceutici S.p.A.  

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TITLE: DOSE-DEPENDENT LUNG FUNCTION IMPROVEMENT AFTER NEBULIZED PORACTANT ALFA ADMINISTRATION TO LUNG-LAVAGED, SPONTANEOUSLY-BREATHING ADULT RABBITS WITH RESPIRATORY DISTRESS

AUTHORS: Ricci F1, Catozzi C1, Murgia X2, Simonato M3, Rosa B1,4, Pieraccini G4, Moneti G4, Lorenzini L1, Bianco F1, Catinella S1, Villetti G1, Civelli M1, Pioselli B1, Cogo P3, Carnielli V5, Dani C6, Salomone F1

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CONTENT:

Nebulized surfactant in combination with nasal continuous positive airway pressure (nCPAP) represents an appealing treatment for preterm infants with respiratory distress syndrome. However, lung deposition after aerosol delivery is usually very low in neonates, accounting for a limited therapeutic effect. Our aim was to determine the required nebulized surfactant dose to achieve an optimal pulmonary response in vivo by means of a customized eFlow Neos vibrating-membrane nebulizer system.

Surfactant deficiency was induced in adult rabbits by repeated broncho-alveolar lavages (BALs). Animals were then managed with nCPAP delivered via customized clinical nasal prongs. Four nebulized surfactant doses, 100, 200, 400, and 600 mg/kg (poractant alfa) were administered with the nebulizer system positioned between the nasal prongs and the Y-piece of the nCPAP circuit. Animals treated with a bolus of surfactant (InSurE) or with nCPAP alone were used as controls (n=9 per each study group). Arterial gas exchange was monitored for 180 minutes, and the oxygenation indexes (OI) was calculated at confirmation of respiratory distress and before sacrifice. Post-mortem, a pressure/volume (P/V) curve was performed and the pressure of the system at 30 ml of air-volume was recorded.

BALs induced a severe respiratory distress in all groups as described by the respiratory distress column in table 1. No signs of recovery were recorded in animals treated with nCPAP alone. Conversely, a dose-dependent improvement of gas exchange was observed in animals treated with nebulized surfactant: the 100 and 600 mg/kg dose were associated only with a modest but significant decrease of OI, whereas the 200 and 400 mg/kg doses elicited a significant decrease of both OI and pressure at 30 ml similar to that observed in the InSurE group (Table 1).

We found a dose-related improvement of oxygenation and pulmonary function after in vivo poractant alfa nebulization. Surfactant doses of at least 200 mg/kg should be used for this treatment.

Table 1. OI values ± SEM at confirmation of respiratory distress before treatment and 180 minutes after treatment. Statistical analysis: 2-ways ANOVA with Tukey’s test. *p<0.01 comparing 180 min after treatment value with respiratory distress value. and Pressure (cmH2O) at 30 ml of air-volume values ± SEM recorded through P/V curve post-mortem.

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Statistical analysis: 2-ways ANOVA with Tukey’s test. *p<0.01 comparing surfactant treatment groups values with nCPAP value.
ID: 430

TITLE: ARTIFICIAL PLACENTA – LUNG ASSIST DEVICE (LAD) FOR PRETERM INFANTS OUTSIDE THE WOMB - EIGHT YEARS OF DEVELOPMENT

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CONTENT:

We report on the latest progress made in the development of a lung assist device in the artificial placenta configuration. The LAD is designed to be solely powered by the neonatal heart and to be connected between the umbilical artery and the vein to provide partial support. It allows newborns to continue breathing while a partial fetal circulation via umbilical artery, LAD circuit, and umbilical vein is established. The LAD has been further miniaturized with high gas exchange and hemocompatibility. The aim of this study is to test the perfusion and blood gas exchange performance of the new LAD in a newborn piglet model.

The LAD consisting of 16 stacked microfluidic blood oxygenators connected via carotid artery and jugular vein (JV) was tested in 3 one-day-old heparinized piglets weighing 1.2 to 1.7 kg. Catheters were placed into the right heart’s atrium (RA) via JV, femoral artery (FA), femoral vein and abdominal vein. Venous access was used for fluids and drugs. Blood gas analysis was done from the LAD inlet and outlet, from RA via JV, and FA. Heart rate (HR) and blood pressure (BP) were measured in the LAD circuit and at FA, SaO2 by pulse oximetry, and extra corporeal blood flow with an ultrasonic transducer. The piglet was ventilated via tracheostomy. A series of hypoventilation cycles were applied over 4 hours. SpO2 target before activating the LAD was 60%. The LAD was tested with oxygen and room air.

Extracorporeal blood flow bypassing the systemic circulation in the LAD (filling volume: ~ 12.5 mL) reached up to 70 ml/kg/min, and the piglet remained cardiovascular (HR: 162±5, mean BP: 77±7) and metabolic (no metabolic acidosis) stable throughout 4 hours. The LAD achieved an oxygen saturation of 100% (470 mm Hg) with support of oxygen and in ambient air more than 90% (90 mm Hg, Figure 1). Arterial blood gases from the FA showed that the LAD could increase SaO2 by more than 30 % (Fig 1). The LAD significantly removed CO2 and consequently the blood pH was increasing from 7.1 to 7.3 when the LAD operated. The total O2 and CO2 exchange is dependent on the flow rate. These in vivo results confirm previous published in vitro findings.

The LAD provided clinically significant gas exchange. The LAD with 16 units achieves blood flow rates through the LAD comparable with one-third of the cardiac output and will be able to provide 50 to 75 % of the oxygen requirements of a preterm infant (0.5-1.0 kg). Further steps in the development of the LAD include the establishment of hemocompatibility using heparin coating and of large bore vascular access via umbilical vessels.

IMAGES:

Fig 1: Blood gases during the in Vivo experiment in the hypoventilated piglet, measured in the femoral artery before (shortcut) and during the lung assist devices operated with oxygen and in ambient air.
COI: None declared
ID: 937  
TITLE: PREMATURITY AFFECTS LUNG DEVELOPMENT IN NEONATAL RABBITS  
AUTHORS: T. Salaets 1; A. Gie 1; D. Dewinter 1; K. Allegaert 1,2; J. Toelen 1  
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CONTENT:  
Improved survival and changing practices in neonatology have altered the phenotype of bronchopulmonary dysplasia (BPD) from a more fibrotic disease to a developmental delay. Nevertheless post-prematurity respiratory disease (PRD) remains an important consequence of preterm birth, although the need for supplemental oxygen was not a good predictor for it. The constant factor in the pathophysiology of BPD and PRD is prematurity, however most of the preclinical research in this field focusses on the effect of hyperoxia or mechanical ventilation, mainly in term rodents. In this study we wanted to evaluate the effect of prematurity alone on lung function and structure in rabbits.  

Rabbit dams were randomized to either a C-section on day 31 (term, alveolar stage of lung development) or day 28 (preterm, saccular stage). Fetal lungs were harvested immediately after birth for morphometry and qPCR in a subset of animals. All others received incubator care (T 32°C, 50% humidity and 21% FiO2), with gavage feeding twice daily. In vivo microCT and X-ray dark field imaging were performed on day 0, 3, 5 and 7 for preterm or day 0, 2 and 4 for term pups. Lung function was measured and lungs were harvested for morphometry on day 7 for preterm pups and on day 4 for term pups (same corrected age).  

At birth preterm rabbit lungs have increased alveolar septal wall thickness (p<0.0001) and a lower total gas exchange surface (p=0.04), in comparison with term rabbits at birth. Preterm fetal lungs exhibit lower mRNA-expression of surfactant protein B and C (p=0.005 and p=0.03). MicroCT reveals a significantly higher proportion of non-aereated lung volume and a higher mean voxel density in the preterm pups in comparison to term pups at all time points, reflecting delayed alveolar recruitment and lung fluid clearance. This is confirmed on dark field images. At the corrected age of 4 days gas exchange surface is smaller in survivors of preterm birth (p=0.02), mainly due to a difference in lung volume (p=0.004). Additionally pups born prematurely had higher values for tissue damping (p=0.008) and elastance (p=0.02) at forced oscillation.  

Preterm rabbits exhibit structural and functional immaturity at birth, which, even in the absence of hyperoxia, lead to persistent pulmonary abnormalities. This shows that preterm birth affects lung development, and advocates for a paradigm shift in preclinical BPD research towards disease models studying prematurity. Further studies should focus on identifying the developmental pathways that are disturbed by preterm birth.  

COI: None declared