Acta Biomed 2012; 83; Supplement 1: 36-39

Original article

Effectiveness of treatment with surfactant in premature infants with respiratory failure and pulmonary infection

Giovanni Vento, M. Tana, C. Tirone, C. Aurilia, A. Lio, S. Perelli, C. Ricci, C. Romagnoli
Department of Pediatrics, Division of Neonatology, Università Cattolica del Sacro Cuore, Rome, Italy

Abstract. *Introduction:* Surfactant inactivation is present in neonatal pneumonia. *Materials and Methods:* One hundred thirty-nine preterm babies with Birth Weight (BW) ≤ 1250 grams were studied and subdivided in two groups: RDS Group, with a diagnosis of "simple" RDS (N 80) and RDS with Pneumonia Group, consisting of babies with a diagnosis of RDS and a positive BALF culture in the first 24-48 h of life (N 59). *Outcomes:* Surfactant administration seems less effective in the latter group, because a significantly higher number of infants needed a second dose of surfactant, compared to the patients suffering from RDS alone. (www.actabiomedica.it)

Key words: surfactant, pneumonia, premature nonates

Introduction

The development of surfactant treatment at the end of the 20th century was one of the great advances in respiratory care (1): the standard treatment of neonatal respiratory distress syndrome (RDS) involves today respiratory support and exogenous surfactant administration. Refinements in surfactant therapy will contribute to ongoing improvement in the 21st century. In this sense, surfactant therapy has been shown to be effective in the treatment of other neonatal respiratory disorders, such as meconium aspiration syndrome, neonatal pneumonia, pulmonary hemorrhage, congenital diaphragmatic hernia or severe respiratory distress in late-preterm infants, along with inhaled nitric oxide and high frequency oscillatory ventilation.

Surfactant and meconium aspiration syndrome (MAS)

It has been shown that the main pathophysiologic factors involved in MAS are: direct toxicity of meconium constituents, effects of inflammatory mediators, protein leak, surfactant dysfunction, alveolar and parenchymal inflammation and edema, altered pulmonary vasoreactivity and airway obstruction. Khammash et al. (2) reported on the treatment of 20 infants with severe meconium aspiration (mean ± SD Oxygenation Index (OI): 37 ± 12), demonstrating that 14 of them had a decrease in the OI of greater than 25% from baseline at 6 hours post instillation following treatment with surfactant. In a post mortem study of 8 infants with meconium aspiration, Dragaville et al. (3) reported that surfactant phospholipid and surfactant protein A content in MAS was not different from that of control subjects. Concentrations of total protein, albumin and membrane derived phospholipid were instead elevated. All infants with MAS had haemorrhagic pulmonary edema, confirming that pathology of MAS is a toxic pneumonitis with epithelial disruption and proteinaceous exudation. Wiswell et al. (4) showed in a group of near-term infants with respiratory failure a significant improvement in gas exchange following the surfactant lavage with KL-4, and a shorter duration of ventilation respect to the Standard Care(SC) Group. The SC patients received therapies including oxygen and con-

ventional positive pressure ventilation, as well as the use of alkalosis, paralysis, vasopressors, or sedation at the discretion of the study site investigator. Rescue therapies, such as high-frequency ventilation, bolus surfactant, inhaled nitric oxide, or ECMO, were not allowed in either group unless patients met treatment failure criteria. Treatment failure for both the Surfaxin and the SC groups occurred when the infant achieved either an OI >25 or an OI that was increased >50% above baseline as ascertained on 2 of 3 blood gas readings within a 3-hour period.

Surfactant and pneumonia

Pneumonia is associated with a substantial leak of plasma proteins into the airways and accumulation of pro-inflammatory cytokines into the lung. It has been shown in different animal models decreased levels of surface-active phospholipids within the alveolar compartment with subsequent Acute Respiratory Distress Syndrome (ARDS) development, after intratracheal injections of lipopolysaccharides (5). In experimental neonatal pneumonia models from *Group B streptococcu*s (GBS) or *Escherichia coli* (EColi), beneficial effects of surfactant administration have been shown in terms of improved lung function and less bacterial growth (6, 7). From a practical point of view, the differentiation of neonatal pneumonia from non-infectious respiratory conditions such as hyaline membrane disease is problematical since the clinical radiological appearance can be identical. As a consequence, it is not possible to study the effects of surfactant for treatment of GBS pneumonia in a prospective, randomized, controlled trial. Although leukocytopenia, increased I:T ratio, and elevated serum CRP develop in the majority of cases within the first 24 hours, there is no way to distinguish with certainty between idiopathic RDS and pneumonia in a premature infant during the first hours after birth, ie, at the time when surfactant therapy should be considered

Materials and Methods

This retrospective study was carried out in our neonatal intensive care unit (NICU) over a 5-years period ending in December 2011. Neonates with Birth Weight (BW) ≤ 1250 grams were studied. They were eligible if inborn and endotracheal intubation at birth was required according to the international American Hearth Association neonatal resuscitation guidelines (i.e. when bag-mask ventilation was ineffective or prolonged) , and on-going intensive care for RDS was required. All the babies were electively ventilated with High-Frequency-Oscillatory-Ventilation (HFOV) delivered by a Draeger Babylog 8000 *plus* ventilator (Dräger, Lubeck, Germany) according to the "optimal" lung volume strategy (8) and received surfactant in the first hours of life (a pig-derived, natural surfactant, Curosurf, Chiesi Farmaceutici, Parma, Italy) at a dose of 200 mg/kg, and a second dose of 100 mg/kg was used if Continuous Distending Pressure was greater than 10 cm H_2O. Babies with mild RDS not requiring surfactant treatment or major congenital malformations were excluded from the analysis. Bronchoalveolar lavage fluid (BALF) samples were obtained in the first 24-48 h of life and were cultured for microbiological analysis including bacteria, Mycoplasma spp, Chlamydia and fungi to diagnose lung infection. Moreover BALF samples underwent to *Candida* Mannan (Mn)Antigen detection by the Platelia *Candida* Ag ELISA immunoenzymatic sandwich microplate assay method (Bio-Rad Laboratories, Hercules, CA) according to the manufacturer's instructions. The assay uses the rat monoclonal antibody EB-CA1, which is directed against the *Candida* Mn molecule. Values of 0.25 ng/mL or greater were considered positive for Mn.

Outcomes

During the study period, 205 preterm babies with BW ≤ 1250 grams were admitted to the III level NICU of Policlinico Gemelli, Università Cattolica S. Cuore in Rome, Italy. Of these, 66 were affected by mild RDS not requiring surfactant administration and were therefore excluded from further analysis. The remaining 139 preterm babies were subdivided in two groups: RDS Group, with a diagnosis of "simple" RDS (N. 80 patients) and RDS with Pneumonia Group (N. 59 patients), consisting of babies with a di-

Table 1. Characterization of infected/colonized infants and non infected RDS Group

	RDS (N. 80)	RDS with Pneumonia (N. 59)	p
Gestational Age (weeks)	27.4 ± 2.0	26.4 ± 1.4	0.001
Birth Weight (grams)	913 ± 232	814 ± 250	0.03
Male	41 (51%)	35 (59%)	0.39
Vaginal delivery	11 (14%)	11 (19%)	0.48
PROM > 12 hours	15 (19%)	22 (37%)	0.01
SGA	13 (17%)	17 (29%)	0.09
Apgar at 5 min	8 [1-9]	8 [3-9]	0.28

Table 2. Major short-term and long-term respiratory outcomes

	RDS (N. 80)	RDS with Pneumonia (N. 59)	p
Newborns requiring > 1 dose of Surfactant	22 (27%)	27 (45%)	0.02
Extubation day	3 [1-24]	7 [1-41]	0.0008
PPHN requiring iNO	0	15 (25%)	<0.0001
Survival	63 (79%)	49 (83%)	0.66
BPD	3:64 (4.7%)	10:50 (20%)	0.01

agnosis of RDS and a positive BALF culture in the first 24-48 h of life. In Table 1 patient's characteristics of the studied infants are shown. In Table 2 major short-term and long-term respiratory outcomes are reported.

In particular, worse respiratory outcomes were observed in the RDS with Pneumonia Group: a significantly higher number of babies required a second administration of surfactant and their median day of extubation was significantly longer, as compared to the patients in the RDS Group. Moreover a diagnosis of persistent pulmonary hypertension of the newborn (PPHN) requiring treatment with inhaled Nitric Oxide (iNO) was made in 15 patients, only in the RDS with Pneumonia Group.

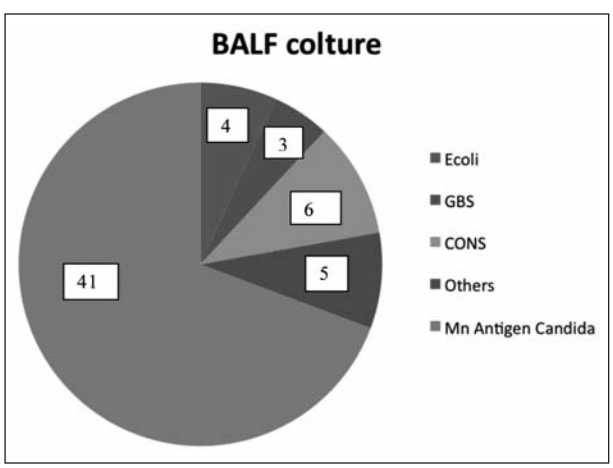

Figure 1. Pathogens isolated from BALF samples in the first 24-48 h of life of RDS with Pneumonia patients, including positive Mn test results

Discussion

Surfactant inactivation is present in neonatal pneumonia and a subgroup of term infants with this condition showed improved oxygenation and reduced need for ECMO in a small, randomized trial of beractant (9). A larger observational study of poractant alfa in infants with group B streptococcal pneumonia showed similar short-term improvements in oxygenation but these were less impressive than those in preterm infants with RDS (10). In our experience, surfactant administration seems less effective in preterm infants with lung colonization/infection at birth, because a significantly higher number of infants

needed a second dose of surfactant, compared to the patients suffering from RDS alone. This could be dependent on the inflammatory response within the lung to several pathogens, including not only bacteria, but also fungi, with subsequent surfactant inactivation. In this sense the *Candida* Mn detection in BALF can diagnose an early status of infection by *Candida spp* in the respiratory tract of preterm newborns and it could reflect an early stage of fetal inflammation/ infection.

References

1. Soll RF. Current Trials in the Treatment of Respiratory Failure in Preterm Infants. *Neonatology* 2009; 95 (4): 368-72.
2. Khammash H, Perlman M, Wojtulewicz J, et al. Surfactant therapy in full-term neonates with severe respiratory failure. *Pediatrics* 1993; 92: 135-39.
3. Dragaville PA, South M, Mc Dougall PN. Surfactant and surfactant inhibitors in meconium aspiration syndrome. *J Pediatr* 2001; 138 (1): 113-5.
4. Wiswell TE, Knight GR, Finer NN, et al. A multicenter, randomized, controlled trial comparing surfaxin (Lucinactant) lavage with standard care for treatment of meconium aspiration syndrome. *Pediatrics* 2002; 109(6): 1081-7.
5. Kennedy M, Phelps D, Ingenito E. Mechanisms of surfactant dysfunction in early acute lung injury. *Exp Lung Res* 1997; 23 (3): 171-89.
6. Herting E, Sun B, Jarstrand C, et al. Surfactant improves lung function and mitigates bacterial growth in immature ventilated rabbits with experimentally induced neonatal group B streptococcal pneumonia. *Arch Dis Childhood* 1997: 76 (1): F3-F8. Special issue.
7. Song GW, Robertson B, Curstedt T, et al. Surfactant treatment in experimental Escherichia Coli pneumonia. *Acta Anaesthesiol Scand* 1996; 40 (9): 1154-60.
8. Tana M, Zecca E, Tirone C, et al.Target fraction of inspired oxygen during open lung strategy in neonatal high frequency oscillatory ventilation: a retrospective study. *Minerva Anestesiol* 2012; 78 (2): 151-9.
9. Lotze A, Mitchell BR, Bulas DJ, et al. Multicenter study of surfactant (beractant) use in the treatment of term infants with severe respiratory failure. *J Pediatr* 1998; 132: 40-7.
10. Herting E, Gefeller O, Land M, et al. Surfactant treatment of neonates with respiratory failure and group B streptococcal infection. *Pediatrics* 2000; 106: 957-64.

Correspondence:
Vento Giovanni, MD
Policlinico A. Gemelli-Università Cattolica S. Cuore
Largo A. Gemelli 8 - 00168 Rome, Italy
Tel. ++39-0630154357
Fax ++39-0630154357
E-mail: vento@rm.unicatt.it