Original Article

Surfactant and Patent Ductus Arteriosus

Abhay Kumar, Anil Lakkundi, Patrick J. McNamara[1] and Arvind Sehgal

Monash Newborn, Monash Medical Centre, VIC, Australia and [1]Division of Neonatology and Cardiovascular Research, The Hospital for Sick Children, Toronto, Canada

ABSTRACT

Objective. To investigate the relationship between surfactant replacement therapy and the development of a haemodynamically significant ductus arteriosus.

Methods. All premature infants at 28-32 wk gestation with a clinical diagnosis of respiratory distress syndrome were retrospectively reviewed and subdivided into two groups; intubated, mechanically ventilated and received surfactant (Group 1); and received nasal continuous positive airway pressure alone (Group 2). The relationship between groups and characteristics of the hemodynamically significant ductus arteriosus was analyzed.

Results. Seventy babies were identified of whom 35 (50%) received surfactant. Babies in group I and II were comparable for gestational age, birthweight, antenatal steroids, gender and fluid intake in first week of life. Babies treated with surfactant therapy were found to be more likely to have a haemodynamically significant ductus arteriosus ($p< 0.01$), larger transductal diameter ($p=0.01$) and increased rate of therapeutic interventions to close the ductus ($p<0.01$). Ventilation parameters (mean airway pressure and fractional inspired oxygen) were higher in group I.

Conclusion. Neonates with respiratory distress syndrome (RDS) who were treated with surfactant replacement are at increased risk of a hemodynamically significant ductus arteriosus that requires therapeutic intervention. Whether the relationship reflects their underlying lung disease or is a direct effect of surfactant requires prospective evaluation. **[Indian J Pediatr 2010; 77 (1) : 51-55]** *E-mail: Arvind.Sehgal@southernhealth.org.au*

Key words: *Patent ductus arteriosus; Surfactant; Hemodynamics*

There is compelling evidence that intra-tracheal surfactant replacement therapy (SRT) reduces the severity of early respiratory disease and both morbidity and mortality associated with respiratory distress syndrome (RDS).[1,2,3,4] Although the effects on oxygenation, pulmonary function and other physiologic indices of respiratory well-being have been extensively researched, the effect of SRT on myocardial performance and hemodynamics is poorly understood. There is data demonstrating a biphasic fluctuation of as much as 22 mm Hg in mean arterial pressure (MAP) after SRT.[5] An inevitable consequence of improved lung compliance is a reduction in pulmonary vascular resistance which may lead to an augmentation in the volume of any systemic-to-pulmonary shunt. There is conflicting data on whether surfactant administration leads to alteration in transductal and pulmonary blood flow or to increased incidence of symptomatic ductus arteriosus.[6,7,8] In a randomized controlled trial of rescue surfactant in infants 29-31 wk gestation, specifically comparing Infasurf (calfactant) and Survanta (beractant), an equal occurrence of ductus arteriosus was noted though the exact incidence was not reported.[9]

While exogenous surfactant therapy has an established role in the management of RDS, the optimal patient population and timing of surfactant delivery remains controversial.[10] Prophylactic therapy offers the advantage of rapidly establishing normal surfactant pools and improving lung mechanics, however, a relative disadvantage is that an infant in whom RDS may not develop may be intubated and may receive a drug that may not be necessary. Selective surfactant therapy avoids the risk of overtreatment by treating only those infants with symptoms of RDS. The disadvantage of selective surfactant therapy is that delayed administration of surfactant allows lung inflammation and protein-containing fluid influx to impair gas exchange further before therapy is provided.[10] Mid-term infants (28-32 wk gestation)

Correspondence and Reprint requests : Arvind Sehgal, Monash Newborn, Monash Medical Centre, 246 Clayton Road, Clayton, VIC 3168, Australia.

[DOI-10.1007/s12098-009-0299-3]
[Received March 03, 2009; Accepted May 13, 2009]

represent a population where benefits of surfactant administration have not been well studied systematically. This population differs in two respects; firstly, the intrinsic risk of respiratory distress syndrome is lower and secondly, many of these patients are successfully managed with nasal continuous positive airway pressure support alone. The risk-benefit ratio has not been well elicited in this population. The goal of this study was to characterize the relationship between SRT and the likelihood of a hemodynamically significant ductus arteriosus (HSDA) necessitating treatment in mid-term neonates.

MATERIALS AND METHODS

A retrospective cohort study was conducted. Subjects were identified by the exposure, not by the outcome. All premature infants who were born between 28-32 wk gestation, over a period between October 2006 and September 2007, and had a clinical diagnosis of RDS were identified from a local electronic database. All neonates with congenital heart disease, chromosomal abnormalities or other complex syndromes were excluded. Neonates were categorized into two groups: neonates who were intubated, mechanically ventilated and received SRT (G*roup I neonates*), and neonates who received nasal continuous positive airway pressure (nCPAP) alone (*Group II neonates*). A diagnosis of RDS was made on basis of oxygen requirement (> 30%) and characteristic chest radiograph features *e.g.,* reticulogranular/air bronchogram pattern. The usual clinical indication for intubation in RDS was increased work of breathing and oxygen requirement greater than 30%. The normal practice at our unit is to administer *Curosurf* TM (poractant alfa) if the FiO2 remained greater than 30% for 30-45 min. All patient health care records were reviewed in a systematic way to obtain details of patient demographics, indices of cardiorespiratory well-being (*e.g.,* apgar scores, ventilator requirements, blood pressure, need for cardiotropes) and clinical characteristics of any symptomatic ductus arteriosus [defined by features of murmur, wide pulse pressure, high ventilatory requirements].

All echocardiography evaluations were performed according to standardized protocols by trained sonographers from the pediatric cardiology department. The decision to perform echocardiography was on the basis of clinical suspicion as highlighted above and not as part of any screening program. The ductus arteriosus was interrogated from a suprasternal notch short axis view and identified using a combination of two-dimensional (2D) and colour flow Doppler imaging. Transductal diameter (2D) and flow pattern (pulse wave Doppler) were calculated according to published methods.[11] The assignment of hemodynamic significance was based on a combination of echocardiographic characteristics as well as the magnitude of the clinical signs of pulmonary overcirculation or systemic hypoperfusion. A HSDA was defined by a transductal diameter > 1.5 mm with echocardiography findings of a significant transductal shunt (*e.g.,* left atrium: aorta ratio > 1.4, unrestrictive transductal flow on pulse wave Doppler with velocity < 1.5 m/sec)[12] and features of pulmonary overcirculation (e.g. increased oxygen or ventilation requirements or increased pulmonary vascular markings) and/or systemic hypoperfusion (*e.g.,* hypotension, metabolic acidosis). Additional factors considered as part of the decision making process included gestational age, and chronological age. All patients with a hemodynamically significant ductus arteriosus were considered eligible for treatment, but the decision to intervene was at the discretion of the responsible physician on the basis of overall clinical impact. The standard approach to treatment was to administer a dose of 0.1 mg/kg indomethacin, once a day for 6 days. Surgical ligation was performed in cases of failure to close after 2 courses or contraindications to medical therapy. Data was also collected on major neonatal morbidities including chronic lung disease (defined as oxygen requirement at 36 wk corrected gestational age), intraventricular hemorrhage and necrotizing enterocolitis according to the usual definitions. The *primary outcome* was the development of a hemodynamically significant ductus arteriosus which required therapeutic intervention. *Secondary outcomes* included the size of the HSDA and age at diagnosis.

Descriptive statistics was used to characterize baseline neonatal characteristics and characteristics of the ductus arteriosus. Parametric (Students t-test) or non-parametric (Mann-Whitney U test) analysis, where appropriate, was performed for continuous datasets. Chi square or Fisher exact test was used to analyze categorical variables between groups. As this study was hypothesis generating, a sample size of convenience was chosen over a one year period.

RESULTS

Seventy patients were identified who met eligibility criteria of whom half were managed by intubation, mechanical ventilation and received SRT (*Group I*) and the rest with nCPAP alone (*Group II*). Neonates in group I had higher mean FiO2 (fractional inspired oxygen) requirement, and higher MAP in first two days of life (Table 1) compared to group II. The overall daily total fluid intake increased from 70.7 ± 10 ml/kg/day on day 1 to 147.3 ± 13.3 ml/kg/day by day 7 but there was no significant difference in fluid intake between

Table 1. Comparison of Neonatal Demographics and Clinical Characteristics. ***Data Presented as Frequency, Median (Interquartile) or Mean ± SD # p < 0.05***

	Group I n = 35	Group II n = 35
Antenatal steroids (n)	83%	85%
Gestational age (weeks)	29.6 (28, 31)	29.5 (28, 31)
Birth weight (grams)	1367 ± 383.2	1389 ± 398.2
Apgar @ 1min	6 (4.2, 6.7)	7 (6, 8)
Apgar @ 5 min	8 (7,9)	9 (8, 9)
Mean FiO2 (%) #	36.5 (30, 47)#	27.5 (25, 31)
Mean MAP (cm H2O)#	9.8 (9, 11)#	7 (6, 7)
Maximal FiO2 (%)#	41 (32, 57.5)#	27 (25, 31)
Maximal MAP (cm H2O)#	10.7 (9.6, 11.4)#	7 (6, 7)
Need for HFOV	3	0
*Pulmonary hemorrhage**	4	0
Metabolic acidosis (pH<7.25 & base deficit > -7)	4	1
Need for cardiotropes	3	1
Aminophylline	32	27
Feeds commenced (day)	3 (2, 5)	2.5 (1, 4)
Full feeds (day)	11 (10,13)	9 (7, 11)
Culture proven sepsis	0	0

MAP-Mean airway pressure, FiO2- Fractional inspired oxygen, HFOV- High frequency oscillatory
ventilation, * includes persistent pink endo-tracheal secretions.

groups. The median age of initial surfactant administration was 2 hours (range) with average number of 1.37 ± 0.59 doses per patient. All echocardiograms were done within 24 hr of the clinical request. All patients had a single echocardiography evaluation before being started on indomethacin. Babies who were treated with SRT had increased transductal diameter and earlier clinical presentation of duct related disease (Table 2). The need for therapeutic strategies to close the ductus arteriosus was also higher in group I. Treated patients received 2 courses of indomethacin except in 2 cases where surgical ligation was performed due to contraindications to medical therapy. Although the numbers are small we identified a significant increase in the rate of chronic lung disease in the surfactant treated group [5/35 (14.3%) *vs* 0/35 (0%)]. Two infants amongst the cohort developed stage II (Bell's staging) necrotising enterocolitis (NEC) both belonged to surfactant group. Eight infants in surfactant group developed intracranial hemorrhage (ICH) (4 - grade I; 2 - grade II; 1 grade IV) while three infants developed ICH in the nCPAP group (all grade I). The differences between groups for NEC and ICH were not statistically significant. There was no difference in mortality between groups.

Table 2. Characteristics of HSDA According to Allocated Group. ***Data is Presented as Mean (SD), Frequency (%) or Median (interquartile range) as Appropriate. HSDA=Hemodynamically Significant Ductus Arteriosus***

	Group I n=35	**Group II n=35**	**p value**
2D echo confirmed HSDA	14 (40%)	6 (17%)	<0.01
Age at diagnosis (days)	4 (3-6)	12 (7-17)	<0.01
Transductal diameter (mm)	2.8 ± 0.6	1.8 ± 0.5	0.014
% of ducts needing treatment	12/14 (85.7%)	0 (0%)	<0.01
Left atrium: aorta ratio	1.84 ± 0.4	1.6 ± 0.3	0.29

DISCUSSION

While causality may not be ascribed, the present study suggests an important association between surfactant replacement therapy and the ductus arteriosus as manifested by increased transductal diameter, earlier clinical presentation and increased likelihood of therapeutic intervention.

Surfactant and Acute Cardiorespiratory Physiology: The hemodynamic consequences of surfactant deficient lung disease include increased pulmonary vascular resistance and both intra- and extrapulmonary shunts. While intra-tracheal administration of surfactant has been shown to improve oxygenation and pulmonary function in preterm animals and infants with RDS,[1,13,14] the systemic hemodynamic consequences are less well understood. In a previous study, the administration of synthetic surfactant to 25 preterm infants led to a significant reduction in pulmonary artery pressure, and increased transductal flow within 15 min of administration, when given between 2-22 (median 4.5) hr of age. These effects were sustained for 1 hr after instillation, and had subsided by 12 hr and were ascribed to its pulmonary pressure lowering effects.[6] Others have suggested that the decrease in pulmonary vascular resistance may be caused by alveolar stabilization and improved oxygenation, release of vasodilator agents from the lungs, or a combination of both.[1] We have recently reported an increase in the ratio of pulmonary to systemic blood flow (Qp: Qs) and ductal size within 30 min of bovine lipid extract surfactant (*BLES*TM) instillation in the delivery room.[15] Alterations in cerebral blood flow after surfactant have also been reported.[16] The magnitude of these hemodynamic changes and the rapidity of their onset may have implications, although longitudinal hemodynamic evaluations after SRT have not been performed and any potential relationship to brain injury has not been investigated.

Surfactant and the hemodynamically significant ductus arteriosus: The focus of the present study was to determine any possible association between SRT and need for treatment of a HSDA. It is reported that of those who were given SRT, 86% received therapeutic intervention for a HSDA; data which is comparable with other studies.[17] The lack of a difference in the LA: Ao ratio between groups is interesting. This may relate to timing of the assessment or alternative reasons for

increased left atrial pressure (*e.g.,* mechanical ventilation, fluid status). Finally, the measurement itself is somewhat subjective and prone to significant measurement error. In a small case series of 10 patients Fujiwara demonstrated a clinically significant ductus arteriosus in all surviving neonates treated with a combined bovine / artificial surfactant preparation. A significantly higher rate of HSDA was identified after human amniotic surfactant administration when compared to a control group of neonates.[13] There is conflicting data on how surfactant alters the timing of presentation of the HSDA although an increased occurrence of HSDA during the early course of RDS has been reported.[6,7] A previous study using porcine surfactant showed no change in pulmonary blood flow and no increase in incidence of HSDA.[8] The discordance in these studies may relate to differences in surfactant preparations, response to treatment or intrinsic patient factors, although these have not been formally evaluated.

The impact of a HSDA should also be considered particularly as the combined effects of chronic pulmonary over circulation and increased need for mechanical ventilation and/or oxygen therapy may have a negative impact on pulmonary mechanics.[18] Recent evidence from an immature primate model demonstrated that early ibuprofen therapy led to normalization of Qp: Qs leading to improved alveologenesis and decreased chronic lung disease changes.[19]

While the present study provides useful information, there are several limitations most notably the small sample size, lack of randomization and retrospective nature of the study design. Although we compared babies who were intubated, mechanically ventilated and received SRT to those managed with nCPAP alone, there is a disparity in respiratory acuity as judged by the need for higher FiO2 and MAP. The development and clinical impact of a HSDA may also relate to underlying disease as respiratory disease itself has been proposed as an important factor in the development of prolonged ductal patency in a previous study.[20] The decision to treat or not was based on a combination of echocardiographic characteristics and clinical state of babies. Retrospective design of the study does not allow standardization for this. It should also be recognized that there is no universally accepted standard of a HSDA.

CONCLUSION

Current management of RDS relies heavily though not primarily on surfactant therapy due to its beneficial effects on oxygenation and pulmonary function. Despite significant advances in respiratory management and neonatal intensive care, the benefits of SRT have not translated into reduced rates of neonatal morbidities. Although the immediate respiratory benefits are obvious clinically, there is a need to be cognizant of potential adverse effects of therapy. The hemodynamic consequences of surfactant administration are likely to be complex but need further investigation. The purpose of the present study is not to dissuade neonatologists from administering surfactant to patients who are likely to benefit treatment, but to highlight the potential association of intervention to a hemodynamically significant ductus arteriosus. It is important, however, that the need for surfactant administration in preterm babies be individualized. Given the potential changes in hemodynamics after SRT, infants should be monitored clinically and where possible, echocardiographically for appearance of a HSDA necessitating treatment.

Acknowledgements

Kaye Bawden, Data Manager, coding and electronic retrieval of data

Contributions: Abhay Kumar, Study design and data collection; Anil Lakkundi, Study design and data collection; Patrick J McNamara, Study design, data analysis, interpretation and draft manuscript; Arvind Sehgal, Study design, data analysis, interpretation and draft manuscript.

Conflict of Interest: None.

Role of Funding Source: None.

REFERENCES

1. Vidyasagar D, Maeta H, Raju TNK, John E, Bhat R, Go M. Bovine surfactant therapy in immature baboons with hyaline membrane disease. *Pediatrics* 1985; 75: 1132-1142.
2. Soll RF. Prophylactic synthetic surfactant for preventing morbidity and mortality in preterm infants. *Cochrane Database Syst Rev* 1998; 2: CD001079. DOI: 10.1002/14651858.CD001079.
3. Soll RF. Prophylactic natural surfactant extract for preventing morbidity and mortality in preterm infants. *Cochrane Database Syst Rev* 1997; 4: CD000511. DOI: 10.1002/14651858.CD000511.
4. Stevens TP, Blennow M, Soll RF. Early surfactant administration with brief ventilation *vs* selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome. *Cochrane Database Syst Rev* 2004; 3: CD003063
5. Hailey GC, Stenson BJ, Laing IA, McIntosh M. Acute blood pressure response to surfactant administration. *Arch Dis Child* 1995; 73: 197.
6. Kappa P, Seppanen M, Kero P, Saraste M. Pulmonary hemodynamics after synthetic surfactant replacement in neonatal respiratory distress syndrome. *J Pediatr* 1993; 123: 115-119.
7. Clyman RI, Jobe A, Heymann M, Ikegami M, Roman C, Payne B, Mauray F. Increased shunt through the patent ductus arteriosus after surfactant replacement therapy. *J Pediatr* 1982; 100: 101-107.

8. Halliday HL, McCord FB, McClure BG, Reid M McC. Acute effects of instillation of surfactant in severe respiratory distress syndrome. *Arch Dis Child* 1989; 64: 13-16.
9. Bloom BT, Clark RH for the Infasurf Survanta Clinical Trial Group. Comparison of Infasurf (Calfactant) and Survanta (Beractant) in the Prevention and Treatment of Respiratory Distress Syndrome. *Pediatrics* 2005; 116: 392 - 399.
10. Stevens TP, Sinkin RA**.** Surfactant Replacement Therapy. *Chest* 2007; 131:1577-1582.
11. Smallhorn JF, Gow R, Olley PM, Freedom RM, Swyer PR, Perlman M, Rowe RD. Combined noninvasive assessment of the patent ductus arteriosus in the preterm infant before and after indomethacin treatment. *Am J Cardiol* 1984; 54: 1300-1304.
12. Sehgal A, McNamara PJ. Does point of care functional echocardiography enhance cardiovascular care in the NICU? *J Perinatol* 2008; 28: 729-735.
13. Fujiwara T, Chida S, Watabe Y, Maeta H, Morita T, Abe T. Artificial surfactant therapy in hyaline-membrane disease. *Lancet* 1980; 1: 55-59.
14. Jorch G, Rabe H, Garbe M, Michel E, Gortner L. Acute and protracted effects of intratracheal surfactant application on internal carotid blood flow velocity, blood pressure and carbon dioxide tension in very low birth weight infants. *Eur J Pediatr* 1989; 148: 770-773.
15. Sehgal A, Mak W, Dunn M, Kelly E, Redington A, Whyte HE *et al*. Impact of prophylactic surfactant on the ductus arteriosus and hemodynamics. Coronary artery perfusion is associated with impaired diastolic dysfunction in preterm infants after PDA ligation. *Paediatric Academic Societies Annual Meeting 2008. Abstract* 5842.23.1.
16. Van Bel F, de Winter PJ, Wijnands HBG, van de Bor M, Egberts J. Cerebral and aortic blood flow velocity patterns in preterm infants receiving prophylactic surfactant treatment. *Acta Paediatr* 1992; 81: 504-510.
17. Heldt GP, Pesonen E, Merritt A, Elias W, Shan DJ. Closure of the ductus arteriosus and mechanics of breathing in preterm infants after surfactant replacement therapy. *Pediatr Res* 1989; 25: 305-310.
18. Gonzalez A, Sosenko IRS, Chandar J, Hummler H, Claure N, Bancalari E. Influence of infection on patent ductus arteriosus and chronic lung disease in premature infants weighing 1000 grams or less. *J Pediat*r 1996; 128: 470-478.
19. McCurnin D, Seidner S, Chang LY, Waleh N, Ikegami M, Petershack J *et al***.** Ibuprofen-Induced Patent Ductus Arteriosus Closure: Physiologic, Histologic, and Biochemical Effects on the Premature Lung. *Pediatrics* 2008; 121: 945 - 956.
20. Reller MD, Ziegler ML, Rice MJ, Solin RC, McDonald RW. Duration of ductal shunting in healthy preterm infants: An echocardiographic color flow Doppler study. *J Pediatr* 1988; 112: 441-446.