ORIGINAL ARTICLE

Surfactant use in premature neonates ≤37 weeks gestation: Experience and outcome at a tertiary care hospital

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Abstract

Objectives: To assess a single-centre experience and outcome of premature neonates who received surfactant therapy.

Methods: The prospective cohort study was done at Shifa International Hospital, Islamabad, from December 2005 to May 2007 and comprised premature neonates (≤37 weeks gestation) who had clinical and radiologic evidence of respiratory distress syndrome and had received surfactant therapy. SPSS 21 was used for statistical analysis.

Results: A total of 52 premature neonates received surfactant. Mean gestational age was 29±2.8 weeks and mean birth weight was 1273±487gms. Only 16(31%) mothers had received antenatal dexamethasone. Surfactant was used as single dose in 41(78%) neonates at 6.1±6.6hours of life or two doses in 11(22%). Chest X-ray and respiratory distress syndrome category showed an overall improvement in 29 (56%) neonates. Complications were seen in 17(33%) neonates, and 21(40%) died. Mortality was significantly associated with gestation (p<0.000) and weight (p<0.008).

Conclusions: Surfactant administration is an option for respiratory distress syndrome in Pakistan.

Keywords: Surfactant, Prematurity, Respiratory distress syndrome, Continuous positive airway pressure. (JPMA 65: 486; 2015)

Introduction

Respiratory distress syndrome (RDS) contributes to morbidity and mortality in preterm neonates mostly in developing countries.[1-3] Mortality is 90% in extreme preterm neonates compared to those in the developed countries. Surfactant administration improves respiratory status of premature neonates, decreases ventilatory requirements, hospitalisation rates and overall outcome. The advent of surfactant therapy has decreased the morbidity and mortality rate from RDS by approximately 50%.[4-8] The current study was planned to assess and share our experience of surfactant use in premature neonates in order to add to the very limited information from developing countries like Pakistan.

Patients and Methods

The prospective cross-sectional study with non-probability convenient sampling was conducted at Shifa International Hospital, Islamabad, from December 2005 to May 2007 at Level IV neonate intensive care unit (NICU). All premature neonates (≤37 weeks gestation) presenting within 12 hours of birth with clinical and radiologic evidence of RDS who received surfactant therapy were included. Excluded from the study were those with dysmorphology, suspected congenital heart disease or surgical conditions, or if there was no parental consent for use of surfactant. The institutional review committee approved the study.

Demographic, clinical, laboratory, radiological and other relevant information were recorded. These included total NICU admissions, premature neonates, age (hours), gender, birth place, birth weight, gestational age (weeks), maternal antenatal dexamethasone use (intramuscular [IM] dexamethasone given as 2 doses of 12mg 12 hours apart), ventilatory parameters before and after surfactant over 24 hours (6, 12, 24 hours), arterial blood gases (ABGs) before and after surfactant, duration of ventilation, extubation rate within 48 hours, overall oxygen requirement after 7 days and RDS category (radiological changes) before and after 24 hours. RDS categories were defined as: Category 1) reduced lung volume with a diffuse reticulogranular pattern, air bronchograms mild or absent; Category 2) reticulogranular pattern more prominent and uniform, lungs hypoaerated with increased air bronchograms; Category 3) progressive opacification of the anterior portions of the lungs with mild obscuration of cardiac silhouette; and Category 4) (lungs appear opaque and display prominent air bronchograms, with total obscuration of cardiomediastinal silhouette.[9]

Surfactant (Survanta,® Abbott Laboratory, Chicago, IL)

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used in the study was given by intratracheal route, 100mg of beractant phospholipids/kg birth weight/dose (4mL/kg/dose), as per manufacturer's instructions and standard protocol. Possible side effects and complications due to use of surfactant and mechanical ventilation (pulmonary haemorrhage, endotracheal tube blockage, intraventricular haemorrhage, pneumothorax and bronchopulmonary dysplasia) were recorded.

All relevant data was recorded using a proforma and data was analysed using SPSS 21. Chi square test was used to compare significant difference in categorical variables in cluding radiological findings, death in different gender, gestational age, exposure to steroids etc. before and after surfactant receipt, and to test associations among variables. Besides, Wilcoxon Sign Rank Test was used to compare the mean values for ventilatory settings and ABG analysis before and after surfactant administration and in different groups. The significance level was set at <0.05.

Results

There were a total of 450 admissions, including 126 (28%) premature neonates, during the study period. Of them, 52 (41%) were given surfactant. The mean age of these neonates at admission was 48 minutes (0.8±1.7 hours; Range: 0-6 hours) (Table-1). The mean Apgar score at 1and 5minutes was 5.7±2 and 7.6±1.7 respectively. Only 16(31%) mothers had antenatal dexamethasone.

Table-1: Demographic and clinical characteristics.

	N	%
Total admissions	450	100
Total Premature	126	28
Clinical RDS	49	39
Surfactant recipients	52	100
Surfactant given as single dose	41	78
Age at time of surfactant	6.1 (±6.6SD)	
Males	37	71
Inborn	43	83
Antenatal dexamethasone	16	31
Single dose of antenatal dexamethasone	7	44
Timing of antenatal dexamethasone	23 hours (±20)	
Mean age at admission	48 minutes (±1.7 hours)	
Mean gestational age	29 weeks (±2.8)	
* <28 weeks	18	34.5
* 28-33 weeks	32	61.5
* 34-37 weeks	2	3.8
Mean birth weight	1273 grams (±487)	
* <750 grams	5	9.6
* 750-1000 grams	14	26.9
* 1000-1250 grams	11	21.2
* >1250 grams	22	42.3

RDS: Respiratory distress syndrome
SD: Standard deviation.

Table-2: Ventilatory parameters* over 24 hours, ABG parameters and RDS severity category premature neonates before and after surfactant therapy.

Ventilator value+ parameters	Before surfactant	After Surfactant 6 hours	12 hours	24 hours	p #
RATE	31±11	31±9.5	30±9.7	26±8	0.04
FiO2	82.7±17	69±21.7	58.8±23	53±20	0.00
PIP	18.8±2	19.2±2.6	19.5±2.7	19±1.9	0.48
PEEP	4±0.3	4.1±0.33	4.8±5.3	4±0.3	0.01
ABG parameters*					
	Before surfactant	**After surfactant**			**p#value++**
pH	7.26±0.2	7.3±0.1			1
PaO2	76±69	107±73			0.29
HCO3	9.98±14	21.3±6			0.18
PaCO2	47±19	48±26			0.59
Severity of RDS on CXR					
	Before Surfactant N (%)	**After surfactant N (%)**			
RDS category9 N (%)					
Normal	11 (21.2)	12 (23.1)			
Grade 1	2 (3.8)	18 (34.6)			
Grade II	9 (17.3)	13 (25)			
Grade III	16 (30.8)	7 (13.5)			
Grade IV	14 (26.9)	2 (3.8)			
Overall improvement		29 (56%)			<0.005

*mean values
+ Wilcoxon Sign Rank Test
#Before surfactant and after 24 hours of surfactant administration
++t- test
FiO2=Fraction of Inspiratory O2 Concentration, PEEP=Positive End-Expiratory Pressure, PIP=Peak Inspiratory Pressure, ABG=Arterial blood gas, pH=measurement of acidity or alkalinity, PaO2=The partial pressure of oxygen, HCO3=calculated value of the amount of bicarbonate, PaCO2=Partial pressure of arterial CO2, RDS= respiratory distress syndrome.

However, the timing of the administration of dexamethasone varied with a mean of 23±20 hours (range: 1-48 hours) before delivery and 7(44%) were given single dose only.

Besides, 49 (94%) neonates had clinical RDS. Radiological features showed moderate to severe RDS (Category 3 or 4) in 30(58%). Surfactant was used as single dose in 41(78%) neonates at 6.1±6hours of life, or two doses in 11(22%). There was significant difference between ventilatory rate before and after 24 hours of surfactant administration ($p<0.05$), Fraction of Inspiratory O_2 (FiO_2) concentration administered before and at 6 hours, 12 hours, and 24 hours respectively ($p<0.0001$), and Positive End-Expiratory Pressure (PEEP)before and at 24 hours ($p<0.05$) (Table-2). However, this difference was not evident statistically for ventilatory rate at 6 and 12 hours, Peak Inspiratory Pressure (PIP) at 6 hours, 12 hours and 24 hours, and PEEP at 6 hours and 12 hours.

ABG analysis showed an improved trend before and after surfactant administration, but was not statistically

Table-3: Association of death after surfactant therapy with demographic and clinical features.

Parameters*	Death		P value
	Yes	No	
Gender			
Male	17	19	
Female	4	11	0.22
Gestational age			
<28 weeks	20	12	
28-33 weeks	1	14	
34-37 weeks	0	4	0
Birth weight	12	6	
500-1000 grams	8	14	
1001-1500 grams	1	10	0.008
>1500 grams			
Maternal dexamethasone			
Yes	4	11	
No	17	19	0.22
Birth Place			
Inborn	18	24	
Outborn	3	6	0.3
Blood culture			
Positive	3	3	
Negative	18	28	0.68

significant. The mean duration of ventilation was 69±59 hours, and 23(44%) neonates were extubated within 48 hours. Oxygen was required for 156±261 hours (or 6.5±11 days) in these neonates. Only 8(15%) neonates required oxygen beyond 1 week. The concentration of oxygen given (30-80%) and documented oxygen saturation of the babies (85-100%) varied. Compared to initial chest X-ray, a follow-up chest X-ray within 24 hours showed an overall improvement in 29(56%), worsening in 5(10%) or remained the same in 5(10%). RDS category showed significant overall improvement (p<0.005) and was significantly improved in males vs females (p=0.003), in-hospital birth vs outborn (p<0.000) and lack of receipt of maternal dexamethasone (p<0.000).

Complications were seen in 25(48%) neonates and included apnoea and bradycardia 17(32%), endotracheal tube blockage 7(13.5%), pulmonary haemorrhage 3(5.8%), intraventricular haemorrhage 3(5.8%), pneumothorax 2(3.8%), infection 3(5.8%), (including pneumonia, sepsis, necrotising enterocolitis) and bronchopulmonary dysplasia 2(3.8%) within 2 weeks. Six (11.5%) neonates had positive blood cultures (3(5.8%) each of acinetobacter spp and enterobacter spp).

The mean duration of hospitalisation was 19.5±15 days with 2(3.8%) requiring re-admission within 7 days of discharge. Overall, 21(40%) neonates died. Of them, 20(95%) were ≤28 weeks of gestation (Table 4). Ten(48%) died within 48 hours and 8(38%) after 168 hours of receipt of surfactant. Mortality was significantly associated with gestation (p<0.000) and weight (p<0.008) but not with gender (p=0.22), receipt of antenatal maternal dexamethasone (p=0.22), birthplace (p=0.30) or bacteraemia (p=0.68). Among the 31 survivors, 13(42%) had more than 6 months follow-up and 2(18%) had recurrent viral illness or wheezing during the first year of life.

Discussion

According to World Health Organisation (WHO), an estimated 1.1 million preterm babies die every year.[1] In the poorest countries, approximately 12% of babies are born prematurely with Pakistan among the top 10 countries. It has one of the highest rates of preterm births (15.8/100 births or 748 100 preterm births per year).[1]

The incidence of RDS from Pakistani studies has been well documented. One study reported RDS in 10% consecutive admissions to the NICU over a 6-year period.[2,10] Among these, 79% required assisted ventilation, had overall mortality 39% and mortality in preterms <1,000 gram was 68%. Another study reported a higher rate of RDS 1.7% of all live births, 37.3% of preterm and 0.11% of term neonates and mortality of 43.6%.[3] A recent study estimated incidence of RDS among preterm neonates to be 35.5% with a mortality of 14%.[11] This may reflect improved overall neonatal care.

Surfactant is one of the expensive modalities for treatment of RDS in premature neonates. But it is proven to be the most effective and standard treatment for RDS in preterm infants in developed countries with significant reduction in mortality and morbidity. Randomised clinical trials have shown that surfactant therapy in RDS results in an overall 40% reduction in mortality and a 35-50% reduction in air leaks.[12-14] Despite the proven and evidence-based literature about the benefits of surfactant, its use is limited, and only few developing countries have reported, including Kuwait,[15] South Africa,[16] India[17] and Iran.[18]

Experience with surfactant in Pakistan has not been reported or published.[2,3,10,11] Only few large teaching and private hospitals across Pakistan have used surfactant in the past, but there is increasing trend over the last few years. Like many countries in the region, the main reason for limited surfactant use is high cost, lack of equipment and experienced personnel. Our small study has demonstrated that it has potential benefit in treatment of RDS with significant radiological and clinical improvement in respiratory distress, but not in ABG analysis. Specifically, rapid decrease in FiO2 and other ventilator parameters at

24 hours indicate lower barotrauma in these babies. This significance was much more for males, being born within the hospital and those who had not received antenatal dexamethasone (data not shown). This implies that antenatal dexamethasone has a role in our population and should be given to all to those at risk.

The high mortality was possibly related to extreme prematurity (95% in ≤28 weeks), severity of RDS (Category 3 or 4 in 58%) and either complications of surfactant or mechanical ventilation. However, mortality in these surfactant recipient neonates is also high in other less-developed countries (21-80%).[16,19]

Limitations of our study were small numbers, lack of control group, limited follow-up and possible other confounders that may have biased our observations.

Since the early experience of this study, we are now much more liberal in using surfactant and have another ongoing study to document improved survival. A multi-centre prospective study from many cities across Pakistan has also been initiated to assess surfactant use with or without other modalities such as conventional ventilation, Nasal Continuous Positive. Airway Pressure (nCPAP) and compare it with no-intervention cases. It will likely shed more light on the specific use of this form of treatment in premature neonates with RDS.

The successful management of RDS depends on early diagnosis and initiation of treatment. Management of RDS includes invasive and non-invasive mechanical ventilation such as nCPAP. Additionally, supplemental oxygen, surfactant administration and availability of support systems such as nursing support, appropriate equipment, X-rays and laboratory support is also important. In developing countries these resources are limited and cost prohibits their routine use. In our cohort of patients, RDS was severe (Grade 3 or 4 in 58%) and so surfactant was probably justified. However, new data suggests that using simple and inexpensive treatments may be more or equally effective in reducing these RDS-related deaths in prematurity.

A recent WHO report says that "inexpensive, proven forms of care for premature babies could save at least three quarters of these babies in the developing world."[1] These include antenatal steroid, "Kangaroo care," antiseptic cream for cord care and antibiotics for sepsis. Increasing concerns about lung damage has prompted a shift to less intensive respiratory support. Now there is emphasis on use of non-invasive ventilation such as nCPAP alone, or nCPAP following initial mechanical ventilation with or without surfactant as an alternative. This use of nCPAP alone has been proven to be cost-effective with equal results. More importantly, trials from developed countries and a Cochrane review have shown that nCPAP groups required less ventilation days and had significantly lower mortality.[20-22] Fewer studies in less developed countries have used this potential cost-effective and life-saving strategy. Small studies from Fiji, Kuwait, India and South Africa have shown advantage with reduction in need for surfactant, mechanical ventilation and mortality.[23-25] It is a simple inexpensive method of "delivering nasal CPAP using nasal prongs to deliver pressurised, humidified, warmed gas (air and/or oxygen) to reduce lung and alveoli collapse". The added advantage is obvious with a fraction of the cost of a conventional ventilator and less technical skills required. These low cost CPAP devices are being developed specifically for low-income countries. The impact of such interventions in premature neonates may be huge with reducing the major killer RDS.[1,24] In Pakistan, low-cost nCPAP should be offered in all premature neonates with mild to moderate RDS.

Conclusions

Surfactant administration was associated with decreased ventilatory requirements, improved respiratory status, chest X-ray findings and early extubation, especially in those with severe disease and >28 weeks of gestation. Surfactant therapy is an option for RDS in Pakistan, but high complication, mortality rates and costs in our setup need further study.

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References

1. March of Dimes, PMNCH, Save the Children, WHO. Born Too Soon: The Global Action Report on Preterm Birth. Eds CP Howson, MV Kinney, JE Lawn. World Health Organization. Geneva, 2012.
2. Bhutta ZA, Yusuf K, Khan IA. Is management of neonatal respiratory distress syndrome feasible in developing countries? Experience from Karachi (Pakistan). Pediatric Pulmonol 1999; 27: 305-11.
3. Ghafoor T, Mahmud S, Ali S, Dogar SA. Incidence of respiratory distress syndrome. J Coll Surg Pak 2003; 13: 271-3.
4. Engle WA. The Committee on Fetus and Newborn. Surfactant-Replacement Therapy for Respiratory Distress in the Preterm and Term Neonate. Pediatrics 2008; 212: 419-32.
5. Katz LA, Klein JM. Repeat Surfactant Therapy for Postsurfactant Slump. J Perinatol 2006; 26: 414-22.
6. Rojas MA, Lozano JM, Rojas MX, Laughon M, Bose CL, Rondon MA, et al. Very early surfactant without mandatory ventilation in premature infants treated with early continuous positive airway pressure: a randomized, controlled trial. Pediatrics 2009; 123: 137-42.
7. Turker G, Koksal N. Complement 4 levels as early predictors of poor response to surfactant therapy in respiratory distress syndrome. Am J Perinatol 2005; 22:149-54.

8. Fuchs H, Lindner W, Leiprecht A, Mendler MR, Hummler HD. Predictors of early nasal CPAP failure and effects of various intubation criteria on the rate of mechanical ventilation in preterm infants of < 29 weeks gestational age. Arch Dis Child Fetal Neonatal Ed 2011; 96: F343-7.
9. Avery ME, Fletcher BD, Williams RG. The lung and its disorders in the newborn infant. Major Probl Clin Pediatr 1981; 1 4th Edition: 1-367.
10. Bhutta ZA, Yusuf K. Neonatal respiratory distress syndrome in Karachi: some epidemiologic considerations. Paediatr Perinat Epidemiol 1997; 11: 37-43.
11. Khan MR, Maheshwari PK, Shamim H, Ahmed S, Ali SR. Morbidity pattern of sick hospitalized preterm infants in Karachi, Pakistan. J Pak Med Assoc 2012; 62: 386-8.
12. Halliday HL. Surfactants: past, present and future. J Perinatol 2008; 28: S47-56.
13. Soll RF. Synthetic surfactant for respiratory distress syndrome in preterm infants. Cochrane Database Syst Rev 2003; 3: CD001149.
14. Seger N, Soll R. Animal-derived surfactant extract for treatment of respiratory distress syndrome. Cochrane Database Syst Rev 2009; 2: CD007836.
15. Victorin LH, Deverajan LV, Curstedt T, Robertson B. Surfactant replacement in spontaneously breathing babies with hyaline membrane disease - a pilot study. Biol Neonate 1990; 58: 121-6.
16. Cooper PA, Saloojee H, Bolton KD, Mokhachane M. Survival of low-birthweight infants at Baragwanath Hospital, 1950-1996. S Afr Med J 1999; 89: 1179-81.
17. Narang A, Kumar P, Dutta S, Kumar R. Surfactant therapy for hyaline membrane disease: the Chandigarh experience. Indian Pediatr 2001; 38: 640-6.
18. Gharebhaghi MM, Sakha SHP, Ghajazadeh M, Firoozi E. Complications among premature neonates treated with Beractant and Poractantalfa. Indian J Pediatr 2010; 77: 751-4.
19. Vidyasagar D, Velaphi S, Bhat VB. Surfactant Replacement Therapy in Developing Countries. Neonatology 2011; 99: 355-66.
20. The SUPPORT Study Group of NICHD: Early CPAP versus surfactant in extreme preterm infants. N Engl J Med 2010; 362: 1970-9.
21. Morley CJ, Davis PG, Doyle LW, Brion LP, Hascoet JM, Carlin JB. COIN Trial Investigators: Nasal CPAP or intubation at birth for very preterm infants. N Engl J Med 2008; 358: 700-8.
22. 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.
23. Pieper CH, Smith J, Maree D, Pohl FC. Is nCPAP of value in extreme preterms with no access to neonatal intensive care? J Trop Pediatrics 2003; 49: 148-52.
24. Koyamaibole L, Kado J, Qovu JD, Colquhoun, Duke T. An evaluation of bubble CPAP in a neonatal unit in a developing country: effective respiratory support that can be applied by the nurses. J Trop Pediatr 2006: 52: 249-53.
25. Sankar MJ, Sankar J, Agarwal R, Paul VK, Deorari AK. Protocol for administering continuous positive airway pressure in neonates. Indian J Pediatr 2008; 75: 471-8.