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Research Article

Mortality and Morbidity Outcomes in Infants Born Less than 28 Weeks Related to Surfactant Doses

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Abstract

Objective: To identify characteristics and outcomes of infants who received multiple doses of surfactant vs those who received one dose.

Methodology: In this retrospective study, we included premature neonates admitted to NICUs in the Mediclinic welcare hospital Dubai from May 2017 till May 2020. Patients were divided into two groups: single dose, and multiple doses. The primary outcome was a composite of death rate or any of the major morbidities, including severe neurological injury, bronchopulmonary dysplasia, or ≥ stage 3 retinopathy of prematurity.

Results: In our study total 127 neonates were enrolled, 35.4% received multiple doses of surfactant. Mean age was 2.6 ± 1.7 hours at time of first dose and 5.6 ± 2.8 hours at time of repeat surfactant dose. Total 34 neonates expired, 70.6% received single dose and 29.7% received multiple doses. Neurological injury was present in 65 neonates, 69.2% received single dose and 30.8% received multiple doses. Broncho pulmonary dysplasia was present in 68 patients, 70.6% received single dose and 29.4% received multiple doses. Third stage of retinopathy was present in 20 patients, all received only single dose of surfactant. Mean duration of ventilation in single dose neonates was 38.6±19.6 hours and 18.2±1.8 hours in those who received repeat dose. Mean duration of bubble CPAP was 72.6±16.1 hours in neonates receiving single dose of surfactant and 50±8.2 hours in those receiving multiple doses of surfactant.

Conclusion: Multiple doses of surfactant was associated with good neonatal outcomes.

Keywords: *Respiratory Distress Syndrome: Surfactant Therapy, Multiple Doses, Death Rate*

Introduction

Premature delivery of neonate is most common cause of admission in neonatal unit for premature care and temperature stabilization. Premature newborn have increased respiratory rate and work of breathing due to reduced production of surfactant necessary for lung expansion and gas exchange in new born premature babies. Other complications of prematurity are developmental delay which can result due to decrease brain development and hypoxia due to respiratory distress [1]. Premature birth before gestational age of 33 weeks has increased risk of morbidity and death which causes psychological distress to parents and increased financial cost of keeping premature in nursery for long duration [2]. In last two decades neonatal care has been improved due to invasive and non-invasive ventilation and formulation of surfactant. These measures have been resulted in increased survival rate and decreased neonatal stay in nursery [3].

Deficiency of surfactant particular feature of premature birth result in increased work of breathing with tachypnea, chest retraction, nasal flaring and/or grunting known as respiratory distress syndrome, which carries increased risk of death and morbidity inform of

pronged oxygen requirement and bronchopulmonray dysplasia. However respiratory distress syndrome can occur in other conditions like transient tachypnea on new born, infection or any cardiac lesion. But in premature newborns most common cause is surfactant deficiency [4].

Extremely premature neonates born before 29 weeks of completed gestational age have severe deficiency of surfactant and lead to prolonged need of oxygen beyond 28 day sof life resulting n bronchopulmonary dysplasia in up to 40% of premature newborn. Bronchopulmonary dysplasia is highly morbid condition [5].

Various intervention has been attempted successfully to reduce incidence and complications of respiratory distress syndrome in premature newborn including administration of antenatal steroid to mother which help in lung maturation and decreases RESPIRATORY DISTRESS SYNDROME. Moreover postnatal prophylactic non-invasive ventilation and surfactant administration through trachea have revolutionized the management of respiratory distress syndrome resulting in decreased morbidity and death rate associated with respiratory distress syndrome in premature neonates. These intervention varies among different centers according to available resources and experience of treating physician [6].

There is difference among neonatologist regarding optimal dosing of surfactant, interval of repeat surfactant administration, invasive/non-invasive ventilation strategy and indication for discontinuation of oxygen therapy. All these practices are dependent according to available resources, experience of treating premature neonates and financial burden bearded by parents. So they vary in different geographical areas or even different in different neonatal units in same circumstances [7].

Administration of artificial surfactant through trachea is break through intervention in treatment of premature babies. Surfactant is given to treat surfactant deficiency in newborn born prematurely. The number of doses are different among different gestational ages and clinical response of surfactant therapy. Surfactant therapy results in extubation from invasive ventilation dn reduced oxygen consumption by increasing lung compliance help in adequate gas exchange at alveoli level. A study conducted in premature newborns found that administration of single dose of surfactant causes decrease oxygen requirement and improved respiratory rate in premature newborns, it prevents risk of pneumothorax. But in small number of children respiratory distress increased after few hours and they need repeat dose of surfactant therapy but does single dose surfactant therapy does not result in decreased death rate [8].

Stevens., *et al.* [9] in found that 20-50% neonates require repeat dose of surfactant therapy after initial surfactant therapy. Death rate was decreased in premature infants who received more than 1 dose of surfactant therapy.

Treatment with surfactant therapy has been changing with development of newer drug formulas and increasing expertise for administration of intra tracheal surfactant. Previously surfactant was given for requiring ventilator support which changed to prophylactic administration in all premature neonates. Prophylactic administration further changed pattern from delayed administration to early surfactant therapy soon after premature birth. Further clinical trial raised question of efficacy of single dose versus multiple doses of surfactant therapy. Some clinicians uses positive pressure ventilation after surfactant administration to improve function capacity while some favored to remove endotracheal tube soon after surfactant administration to avoid pneumothorax [8].

Still there is lack of data on number of surfactant doses in order to reduce death rate, need for ventilation and need for non-invasive oxygen therapy. This study was aimed to determine to find clinical outcomes of single dose surfactant therapy versus multiple dose surfactant therapy in terms of reduced death rate and less need for ventilation therapy in premature newborn of less than 28 week of gestation.

Objective

To compare the frequency of death rate and morbidity in infants born less than 28 weeks related to number of surfactant doses.

Materials And Methods

Study design

Retrospective Cross sectional study.

Study setting

Department of Neonatology, Mediclinic welcare hospital Dubai

Study duration

May 2017 to May 2020.

Patient selection

Total 127 premature neonates born before 28 weeks of gestation of either gender admitted in Department of Neonatology, Mediclinic welcare hospital Dubai from May 2017 to May 2020, due to respiratory distress syndrome and received single or multiple doses of surfactant therapy were enrolled using **c**onvenient sampling. Neonates with congenital cardiac defects, diaphragmatic hernia, syndromic neonates and septic neonates were excluded from study.

Data collection procedure

Medical record of neonates full filling the inclusion and exclusion criteria was reviewed after approval from hospital ethical board, while patients' consent was needed because it was retrospective analysis of medical record. Demographic data regarding maternal age, neonatal age at time of giving surfactant, gestational age, gender, history of infection in mother and type of delivery was noted. Most of patients received poractant alfa (Curosurf, Chiesi USA Inc., Cary, NC, USA) The indication of intratracheal surfactant therapy was decided in line of our hospital guideline and uniformity was maintained to avoid biasness and maintain safety of premature lowbirth newborns.

"These recommendations suggest administration of surfactant to intubated patients with respiratory distress syndrome (grade A evidence), prophylactic administration after stabilization in intubated preterm neonates at significant risk of RESPIRATORY DISTRESS SYNDROME (grade A evidence), repeat administration to neonates who have persistent or recurrent need for oxygen within the first 72 h of age (grade A evidence), and retreatment to be considered when oxygen requirement is >30% within 2–6 h after administration of the first dose (grade A evidence)." Patients were divided into three groups: no surfactant, single dose, and multiple doses. The majority of surfactants were administered in the endotracheal tube.

Outcomes

The primary outcome was a composite of death rate prior to discharge or major morbidity. Major morbidities included severe neurological injury, bronchopulmonary dysplasia (BPD), and severe retinopathy of prematurity (ROP). Severe neurological injury was defined as the presence of grade 3 or 4 intraventricular hemorrhage or persistent periventricular echogenicity on head ultrasound [8]. BPD was defined as the receipt of any respiratory support at 36 weeks' postmenstrual age or at the time of discharge to a level 2 hospital [8]. Severe ROP was defined as stage 3 or higher retinopathy or treated retinopathy (laser or injection therapy) in either eye [8]. Data was entered in specially designed proforma.

Statistical analysis

Data was entered and analyzed by using SPSS version 22.0. Mean and standard deviation were calculated for quantitative variables while frequency and percentage were calculated for categorical variables. The maternal and infant characteristics were compared among the three groups using the Chi-square test for categorical variables and ANOVA analysis for continuous variables. P value ≤ 0.05 was taken as statistical significant.

Results

In our study total 127 neonates were enrolled, 35.4% received repeat dose of surfactant. Mean age was 2.6 ± 1.7 hours at time of first dose and 5.6 ± 2.8 hours at time of repeat surfactant dose. There were 51 males and 31 females who require only single dose while repeat dose was given in 10 males and 35 females (Figure 1). Mean gestational age was 25.4 ± 1.1 in single dose group and 24.7 ± 0.63 in multiple dose groups. Mean birth weight was 811.34 ± 95.3 grams in single dose group and 755.11 ± 23.1 grams in multiple dose group. Neonates who require only one dose of surfactant had history of maternal hypertension in 66.7%, antenatal steroid cover in 61.2%, maternal diabetes in 89.4%, birth by C-section in 49.3%, maternal chorioamniotis in 28.6%, APGAR score less than 7 in 67.7% and resuscitation in 60.9% patients. Total 34 neonates expired, 70.6% received single dose and 29.7% received multiple doses. Neurological injury was present in 65 neonates, 69.2% received single dose and 30.8% received multiple doses. Broncho pulmonary dysplasia was present in 68 patients, 70.6% received single dose and 29.4% received multiple doses. Third stage of retinopathy was present in 20 patients, all received only single dose of surfactant. Mean duration of ventilation in single dose neonates was 38.6 ± 19.6 hours and 18.2 ± 1.8 hours in those who received repeat dose. Mean duration of bubble CPAP was 72.6 ± 16.1 hours in neonates receiving single dose of surfactant and 50 ± 8.2 hours in those receiving multiple doses of surfactant.

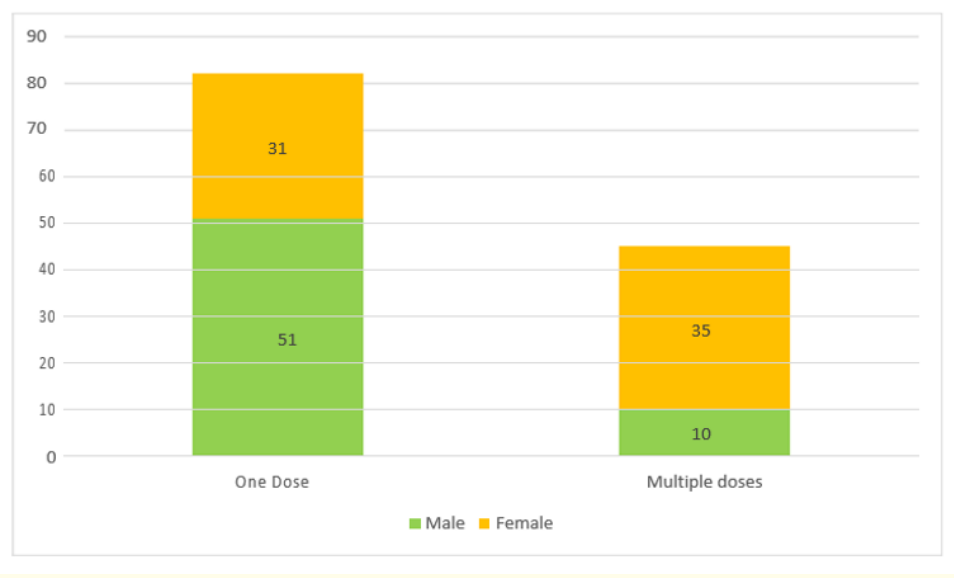

Figure 1: *Gender distribution.*

Discussion

Almost two decades ago prophylactic administration of surfactant was advocated along with hypothesis of improved outcome after more than single dose of intra tracheal surfactant therapy [10]. The aim of this study was to determine outcomes of single dose and multiple doses of surfactant therapy in treatment of RESPIRATORY DISTRESS SYNDROME in premature newborns requiring surfactant therapy.

Baseline characteristics Single dose		Surfactant		Total	p-value
		Multiple doses			
Gestational age		25.4 ± 1.1	24.7 ± 0.63		< 0.001
Birth weight		811.34 ± 95.3	755.11 ± 23.1		< 0.001
Maternal hypertension	Count	30	15	45	0.714
	%	66.7%	33.3%	100.0%	
Ante natal steroids	Count	63	40	103	0.097
	%	61.2%	38.8%	100.0%	
Maternal diabetes	Count	42	5	47	< 0.001
	%	89.4%	10.6%	100.0%	
Birth by C-section	Count	34	35	69	< 0.001
	%	49.3%	50.7%	100.0%	
Maternal chorioamniotis	Count	14	35		< 0.001
	%	28.6%	71.4%		
APGAR score less than 7 at 5 minutes	Count	42	20	62	0.465
	%	67.7%	32.3%	100.0%	
Resuscitation	Count	39	25	64	0.389
	%	60.9%	39.1%	100.0%	

Table 1: *Baseline characteristics.*

Outcomes Single dose		Surfactant		Total	p-value
		Multiple doses			
Death rate	Count	24	10	34	0.391
	%	70.6%	29.4%	100.0%	
Neurological injury	Count	45	20	65	0.152
	%	69.2%	30.8%	100.0%	
Broncho pulmonary dysplasia	Count	48	20	68	0.05
	%	70.6%	29.4%	100.0%	
Third stage of retinopathy	Count	20	0	20	<0.001
	%	100.0%	0.0%	100.0%	

Table 2: *Outcomes.*

	Surfactant	N	Mean	Std. Deviation	Std. Error Mean	P-Value
Duration of ventilation	Single dose	82	38.63	19.6	2.16	<0.001
	Multiple doses	45	18.22	1.8	0.28	
Duration of CPAP	Single dose	82	72.60	16.1	1.78	<0.001
	Multiple doses	45	50.00	8.2	1.23	

Table 3: *Mean duration of mechanical ventilation and CPAP.*

In our study total 127 neonates were enrolled, 35.4% received multiple doses of surfactant. Mean age was 2.6 ± 1.7 hours at time of first dose and 5.6±2.8 hours at time of repeat surfactant dose. There were 51 males and 31 females who require only single dose while repeat dose was given in 10 males and 35 females.

Stevens., *et al.* [9] in found that 20 - 50% neonates require repeat dose of surfactant therapy after initial surfactant therapy. Death rate was decreased in premature infants who received more than 1 dose of surfactant therapy.

While in a study conducted by Cochal., *et al.* [10] repeat dose of intra tracheal surfactant was given in 35% premature infants in order to treat respiratory distress syndrome. Premature new born with antenatal history of maternal chorio-amniotis was associated with increased rate of repeat dose of surfactant therapy i.e. 71.4% needed repeat dose while newborns with no maternal history of infection needed repeat doe in 28.6%. These findings were consistent with our finding of increased need of repeat surfactant therapy in newborns having antenatal maternal infections.

Tsakaldis., *et al.* [11] found that respiratory distress recurred after 6 hours of first dose of surfactant therapy. They compared twenty eight premature infants of less than 32 weeks of gestation who received multiple doses with 98 premature neonates who received single dose of surfactant therapy. Infants with antenatal history of maternal chorio-amniotis needed more doses of repeat surfactant therapy. These finding were also similar to result sof our study. Herting., *et al*. [12] hypothesized that after infection with group B streptococcal organism and chorioamnionitis there is increased rate of repeat surfactant administration due to inactivation of inflammatory mediators which causes more severe respiratory distress and need for repeat surfactant therapy.

Katz., *et al*. [13] in his study enrolled premature newborns with birth weight of less than 1kg having respiratory distress syndrome to determine risk of atelectasis. Total one hundred and sixty five preterm low birth neonates were included in study. Among study participant thirty nine premature low birth weight babies were not given any dose of surfactant therapy having mean gestational age of 27.7 week and mean birth weight of 0.856 kg, while one hundred and sixteen premature low birth neonates were given single dose of intra tracheal surfactant therapy having mean gestational age of 26 weeks and mean birth weight was 0.751 kg and twenty five infants with mean gestational age of 24.7 weeks and mean birth weight of 0.647 kg received repeat dose surfactant due to atelectasis. The need for repeat dose was found in neonates with less gestational age just like recorded in results of our study where less gestational age was associated with repeat surfactant dose.

Moreover Katz., *et al.* [13] also found that preterm low birth weight received ante mater corticosteroid needed only single dose of surfactant which is consistent with our results of protective effect of antenatal steroids in premature low birth neonates. The neonates given multiple doses had good outcomes in terms of decreased death rate, brain injury, broncho pulmonary dysplasia and third stage of

retinopathy which reflect that keep low threshold for repeat dose improves clinical outcomes of neonates having respiratory distress due to surfactant deficiency.

In a randomized trial, Corbet., *et al.* [14] lower death rate and lower rates of necrotizing enterocolitis were reported in premature neonates receiving multiple surfactant doses as compared to premature neonates given single dose of surfactant therapy. These finding showed that multiple doses of surfactant resulted in decreased morbidity and mortality in premature low birth neonates admitted in neonatal unit.

In a Cochrane review of three randomized trials, Soll and Ozek identified lower risks of pneumothorax and death rate associated with multiple doses of surfactant [15]. In a multivariate logistic regression analysis, four risk factors were independently associated with failure of surfactant therapy: GA < 28 weeks, C reactive protein ≥ 10 mg/L, absence of antenatal corticosteroids and lower surfactant dose. Infants receiving 200 mg/kg surfactant had a failure rate of 14% versus 35% with surfactant dose < 200 mg/kg [16] Challis., *et al.*

[17] Studied 5209 infants who received 7980 surfactant administrations, late surfactant treatment (> 2 hours after birth) was provided for 39% of very preterm infants and associated with higher neonatal morbidity. While in other studies no differences in the incidence of preterm morbidities among different types of surfactant therapy was found [18-22].

However study by Cochal., *et al.* [10] reported opposing results as compared to our study and reported increased odd of death rate and morbidities in low birth premature infants who received multiple doses of surfactant and these morbidities were dose related. These difference can be attributed to timing of surfactant therapy because they gave surfactant late during course of treatment while we gave surfactant early during treatment which resulted in favorable outcome in premature newborns. The difference in timing of giving surfactant is highly variable in different hospital setting due to lack of consensus of surfactant administrating guideline [23,24].

Overall, these findings support the concept that multiple surfactant doses

Conclusion

It was concluded that administration of multiple doses of surfactant therapy of premature neonates having respiratory distress syndrome has good outcomes in term of decreased morbidity, brain injury, broncho pulmonary dysplasia and retinopathy of prematurity. Clinician should keep low thresh hold while administrating surfactant therapy.

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Volume 11 Issue 2 February 2022