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Characteristics and Clinical Outcomes of Preterm Neonates with RDS According To Number of Doses of Surfactant

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Abstract
This study was conducted in a tertiary care center over a period of one year with a aim to study antenatal ,neonatal and postnatal factors modulating surfactant need in preterm newborns with RDS and also to find out the odds of mortality and morbidity in those children with surfactant administration. This prospective study successfully documented that neonates with history of antenatal steroid to mother and maternal hypertension had lesser need of surfactant treatment against those neonates with maternal diabetes who were found at higher end of requirement of surfactant. Extreme preterms(<28week GA) had higher need of multiple surfectant dose(42.8%). Neonates given multiple surfactant had higher morbidity(57%) as well as mortality(28.5%) finding suggests that receipt of multiple surfactant doses could potentially be a useful marker for severe underlying respiratory immaturity and could be used to identify patients who should be closely monitored to prevent ongoing lung injury and other adverse outcomes.

Keywords: *surfectant, RDS, extreme preterme, maternal hypertension*

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I. Introduction

In developing countries, neonatal mortality account for more than one third of under five mortality [1] with higher deaths occurring in the early neonatal period i.e. 25%–45% occurring in the first 24 hours, and about 75% during the first week of life [1,2]. Respiratory distress syndrome (RDS) or hyaline membrane disease (HMD), has been recognized as the most common co-morbidity of prematurity. Over half of those with extreme/very low birth weight (between 500-1500 grams) show clinical signs of RDS as well [3, 4]. Surfactant production is insufficient due to the immature development of type II pneumocytes, which begin to produce surfactant at approximately 20 weeks gestation [5]. Insufficient surfactant leads to reduced pulmonary compliance and increased surface tension [6 7]. This results in increased risk of alveoli collapse at expiration followed by reduction in total surface area for gaseous exchange, as well as the alveolar-capillary diffusion capacity. Hypoxia and hypercapnia develops. The risk and severity of RDS are inversely proportional to the gestational age of the infant at birth [8]. In fact, prior to the introduction of surfactant, RDS was considered to be the leading aetiology of mortality in preterm infants [9]. As a result, much effort has been focussed on the prevention and treatment of RDS.

The beneficial impact of surfactant has led to enhanced development and research into new surfactant analogues [10]. Two main subtypes have been developed: natural and synthetic. Animal-derived surfactant, also known as natural surfactant, contains a similar morphology to that of human surfactant. Natural surfactant has been considered the superior subtype, due to its greater efficacy in mimicking the action of human surfactant. Animals used in this process include pigs and cows. There are three commonly researched natural surfactants [11].poractant beractant calfactant.Despite the positive findings when natural surfactant is administered, there are a number of drawbacks, including the lack of cost-effectiveness, inconsistent efficacy etc.

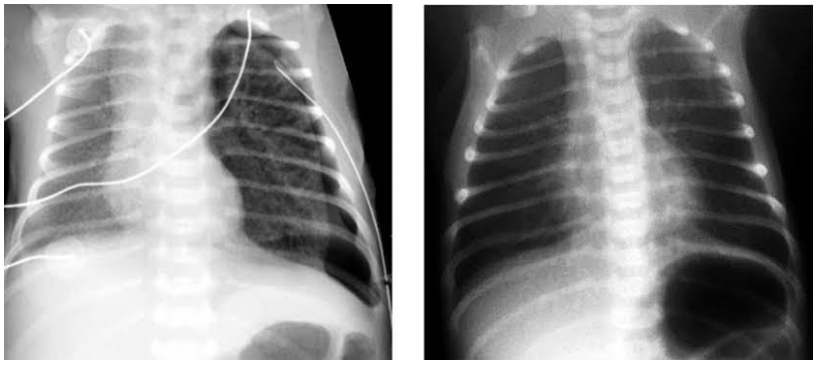

Fig1 :Images of chest xray in neonate with RDS before surfactant(left side)and after surfactant(right side)

Surfactant composition is derived from 90% phospholipid and 10% protein. Phosphatidylcholine (PC) is the main phospholipid class, with dipalmitoylphosphatidylcholine (DPPC) the commonest subtype. Monolayers of DPPC are crucial in the maintenance of surface tension at near zero levels during compression [12]. Surfactant protein A, B, C and D (SP-A, -B, -C and -D) are the four key proteins that have been isolated. SP-B and -C, on the other hand, play an intricate role in sustaining alveolar ventilation. Because of their small hydrophobic properties, SP-B and -C interact with polar head groups of DPPC to form a surface-active film, which lowers surface tension and allows alveoli to maintain patency. SP-B, in particular, is crucial in the maturation of surfactant. SP-B gene expression is actually prevalent at 24 weeks gestation but maturation onset only occurs at 30 weeks gestation [13].Multiple doses of surfactant administration are often needed in extreme preterms with HMD grade 3 or 4. Our study aiims to find the charecteristics and outcomes in neonates with surfactant administration.

II. Materials And Methods

The study was conducted over a time of 1 year from January 1 2020, to December 31 2020 in a tertiary care centre.

1. Aiims and objectives

1. To study the antenatal, natal and postnatal charecters of new-borns demanding surfactant therapy .
2. To study the outcomes in terms of morbidity as well mortality in all neonates given surfactant.
3. To study the requirement of surfactant in preterm newborns with RDS.

2.Eligibility criteria

INCLUSION CRITERIA

1.Neonates born at <36weeks' gestation with HMD or RDS.

2 Admitted to NICU of tertiary care hospital between January 1, 2020 and December 31,2020 were included.

- Infants were divided into three groups based on surfactant dosage: no surfactant, single dose, and multiple doses.

EXCLUSION CRITERIA

- Neonate more than 36 week
- Infants with major congenital anomalies
- Moribund at admission for whom palliative care was provided immediately after birth were excluded from the study.
- Neonates with surfactant administration in respiratory distress due to causes as severe MAS, congenital pneumonia.

3.TYPE OF STUDY

It was a Prospective and analytical study done over a period of one year and enrolling all eligible neonates with RDS who received surfactant therapy.

4.DATA COLLECTION

Data was collected and was entered in the excel sheet in detail involving prenatal, natal and postnatal factors involving the neonate. SNCU case sheet and Labour room call sheets were used for recording the information along with history elucidated from relatives. Data were processed and reports were expediated. It was documented in a systematic manner and analyzed using appropriate statistical methods.

5.METHODS

Surfactant therapy administration was according to recommendations made by national guidelines(NNF India guideline) to ensure safety and accuracy. All aseptic precautions were followed and informed consent of parents were taken prior to surfactant administration.

For surfactant administration Insure technique was followed. Neonates were intubated with appropriate sized ET tube and surfactant administration was done according to recommended dose i.e 200mg/kg on first administration and 100mg/kg dose used for subsequent second and third doses(wherever given).
Decision regarding surfactant administration was done depending on the severity of RDS in neonates:

- Prophylactic administration(14) [15]after stabilization within 15 minutes after birth was done in neonates with GA <26wk and also in 26-30 wk if no antenatal steroids were given or the neonate needed intubation anyway.
- Early rescue therapy was done preferably within 60mins of birth in neonates <30 wk GA with signs of severe RDS(audible grunting, severe tachypnea and subcostal or intercostal indrawing persisting even on CPAP or FI02 requirement of more than 40% on CPAP)

- Treatment of established RDS was done irrespective of gestational age as early as possible, mostly within 12hours of birth(earlier in inborn patients) in all neonates whose CXR suggested of changes of HMD grade 2 or more or they needed ventilatory support or at least 40% requirement on machine **cpap**.
- Retreatment was considered when oxygen requirement was >40% within 2–6 h after administration of the first dose
- Repeat administrations were given to neonates who have persistent or recurrent need for oxygen within the first 72 h

Patients were divided into three groups based on the number of doses of surfactant given:

1. no surfactant,
2. single dose,
3. multiple doses.

- The primary outcome was a composite of mortality 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]. 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. Severe ROP was defined as stage 3 or higher retinopathy or treated retinopathy (laser or injection therapy) in either eye. Secondary outcome was individual components of composite outcome.

III. Results

The study was conducted with a total 100 patients with RDS and they were divided into three categories depending on the administration of surfactant: no surfactant 50, single dose of surfactant given in 43 patients and multiple dose in 7 patients.

Table 1: sex distribution of neonates in study population

Doses of surfactant	Male child	Female child
No	26(52%)	24(48%)
Single	25(58%)	18(42%)
Multiple	3(42%)	4(58%)

Fischer's exact test p=0.0312

From our study we found out of total study population 54(54%) neonates were male and rest 46(46%) were female out of which 26(52%) male were among neonates with no surfactant application, 25(58%) among those given a single dose of surfactant and 3(42%) among neonates with multiple dose.

Table 2 Maternal factors and effect on neonatal outcome in neonates with RDS

Variables	No surfactant (n=50)	One dose(N=43)	Multiple dose (n=7)	P value
Maternal hypertension	15(30%)	10(23%)	1(14%)	P=0.58
Maternal diabetes	6(35%)	9(53%)	2(12%)	P=0.02
Antenatal steroid	34(68%)	15(34.8%)	1(14%)	P<0.0065

[Total 17 IDM infants were enrolled in our study][test used is Chi square test]

From the study it was seen that out of neonates whose mother had maternal hypertension: 30%(15)were not given surfactant while one dose given in 23%(10) and those needing multiple doses were 14%(1) neonate. In terms of maternal diabetes: 53% (9)neonates needed one dose and 12%(2) needed two doses of surfactant wheras 6(35%) neonates of diabetic mother were not given any surfactant. Amongst Babies whose Mothers were given Antenatal steroids 68% (34) were not given any surfactant while 34.8%(15) needed only one dose and 14% (1)required 2 doses of the same. Need of increased surfactant administration in infants of diabetic mother i.e diabetes in mother being a risk factor for surfactant requirement(p=0.02)and less surfactant requirement in neonates who received antenatal steroids(p,<0.0065) was found statistically significant in study.
Table 3.Natal factors and effect on neonates with RDS

Timing of administration first surfectant <6h 6-12h 12-24h >24h	No surfactant _ _ _ _	Single dose 9(20.9%) 7(16.2%) 20(46.5%) 7(16.2%)	Multiple doses 2(28.5%) 1(14.2%) 4(57.1%) 1(14.2%)	P value P=0.67
Gestation age (weeks) mean	34wk	30 wk	27 wk	----
GA 26-28wk	0	4(9%)	3(42.8%)	P=0.02
GA 28-32wk	3(6%)	25(58%)	2(28%)	
GA 32-36 wk	47(94%)	14(32.5%)	2 (28.6%)	
LSCS	27(54%)	13(30.2%)	3(42.8%)	P=0.6626
Outborn	32(64%)	28(65.1%)	4(57.6%)	P=0.92

Chi square test undertaken

Out of LSCS delivered neonates those needed surfactant 30.2%(13) needed single dose,42.8%(3) needed multiple dose and 27(54%) no surfactant. Among outborn patients it was seen that 64%(32) had no need of surfactant, 65.1%(28) needed one dose with 57.6%(4) had multiple dosing. From the study it was found that out of total neonates those being given single dose surfactant 20.9%(9) of them were given within 6hours of birth,16.2%(7) within first 6 hours of birth, 46.5%(20) within 12-24hrs of life and 16.2%(7) after 24hours of life. Whereas those babies needed multiple surfactant dosing 28.5%(2) were given first dose within 6hrs of life,14.2%(1) within 6-12hrs,57.1%(4) within 12-24hrs of life and 14.2%(1) beyond 24hrs of life.In terms of mean gestation age, no need of surfactant was seen in a mean of 34wk, with one dose needed in 30wk mean GA and multiple dose in 27wk neonates. In terms of gestation age neonates of 32-36wk had no surfactant administration in 94% cases (47),32.5% (14) were given one dose of surfactant and 28.6%(2) were given multiple doses. In gestation week 26-28 wk 9% (4) needed single dose and 3(42.8%) needed multiple doses wheras no neonate was found in the category of no dose of surfactant requirement. In gestation age of 28-32 wk 6%(3) belonged to category of no surfactant, 58%(25) in single dose, 28%(2) in multiple doses requirement category.

Among the above natal factors statistically proven correlation was spotted among surfactant requirement and gestational age of the neonate ,more demand of surfactant with earlier gestational age was seen (p=0.02).

Table4. Postnatal factors and contributing to neonatal outcome in RDS

Variables	**No surfactant**	**Single dose**	**Multiple doses**	**P value**
Birth weight(mean)	1520gm	1028gm	900gm	-------
Patients who were given extensive cardiopulmonary resuscitation	2(4%)	6(14%)	2(28%)	P=0.066
Small for gestation age	24(48%)	22(51.1%)	1(14.2%)	P=0.024

In postnatal features of neonates it was seen that Mean birth weight was 900gm in those needing multiple surfactant dosing as against 1028 gm needing single dose and 1520gm as mean weight with no surfactant dose. In group of IUGR babies 24(48%) had no need of surfactant dosing, 51.1%(22) had need of single dose and 14.2%(1) had need of multiple doses. Out of all patients who were resuscitated extensively 4%(2) belonged to category of not in demand of surfactant, 14% (6)of those needed single dose of surfactant was resuscitated actively,28%(2) of patients needed active resuscitation belonged to category of multiple surfactant dose requirement.

From our study we found that in postnatal factors of neonate influencing need of surfactant therapy significant correlation was there among children with intrauterine growth retardation and surfactant dosing(p=0.024).IUGR babies had almost equal need of surfactant therapy as AGA babies. Whereas the relation between the need of surfactant in actively resuscitated newborn was found to be statistically insignificant.

Primary Neonatal outcome in RDS patients

Outcome	No surfactant(n=50)	Single dose(n=43)	Multiple doses(n=7)
Mortality	4(8%)	3(6.9%)	2(28.5%)
Discharge with morbidity	4(8%)	7(16.2%)	4(57%)
Discharge without morbidity	42(84%)	33(76.7%)	1(15%)

p value=0.023.

Among the patients enrolled for study 8%(4) mortality was found among neonates who were not given any surfactant wheras mortality was 6.9%(3) in single dose of surfactant administration and 28.5%(2) in multiple doses of surfactant administration. Patients who were discharged with one or more morbidity accounted to 8%(4) in category of no surfactant administration, 16.2%(7) among neonates given single dose and 57%(4) among those received multiple surfactant doses. Neonates who were discharged successfully without any morbidity were 84%(42) in no surfactant group, 76.7%(33) in single dose surfactant group whereas only 15%(1) in those received multiple administrations of surfactant. The correlation among primary outcomes in neonates with RDS who were given surfactant was found to be statistically significant as well(p=0.023)

Secondary outcomes in neonates with RDS with surfactant administration

Variables	No dose	Single dose	Multiple dose
BPD	1(2%)	3(6.9%)	2(28.5%)
Pneumothorax	0	1(2.3%)	1(14.5%)
Rop	0	0	1(14.5%)
Ivh	2(4%)	2(4.6%)	1(14.5%)
Prolonged need of invasive ventilation	1(2%)	1(2.32%)	3(42.8%)
Expired	4(8%)	3(6.9%)	2(28.5%)

Chi square test p=0.99

From the data obtained it was found that morbidity and mortality were more among the neonates needing multiple dose of surfactant as compared to those with single or no surfactant administration. Incidence of ROP(grade 2 or more) 14.5%(1) aslo BPD 28.5%(2),pneumothorax 14.5%(1),need for prolonged invasive ventilation 42.8% (3), IVH (1)14.5%was more in those needing multiple surfactant dosing as compared to those with single dose of surfactant where mortality was 6.9%(3), ivh was 4.6%(2), BPD 6.9%(3), pneumothorax 2.3%(1). Whereas all mortality and morbidity was least incident in those group that didn't receive any surfactant dosing. Statistical correlation among the morbidity profile and surfactant dosin g was not considerable.

IV. Discussion

1.Sex distribution in study population : An ongoing theme throughout the literature is that males tend to develop RDS and CLD at a much higher rate than their female counterparts.Amongst the study population, overall total male neonates 54 and female neonates were 46 out of which total male: female ratio who needed surfactant administration was found to be 1.2 ($p<0.05$) hence male neonates were found to be more susceptible and in need of surfacatant treatment. Similar result was documented in a metaanalysis by Liptzin et.al including data from over 500,000 preterm newborn infants highlighted a sex ratio of 1.56–1.84 ($p < 0.05$) in favour of males for respiratory distress.[16-17]female fetuses tend to weigh more at any given gestational age and thus tend to have more alveoli and alveolar surface area than gestational age-matched females (18). Surfactant production, has

also been shown to appear earlier in female lung development than in males(19). Fleisher et al. also confirmed the same (20).

2. Prenatal factors and surfactant requirement:

A)among the prenatal factors significant correlation was found in neonate born to mother with diabetes requiring surfactant administration in preterm with RDS($p<0.05$) 53% neonates of diabetic mother ended up needing one dose and 12% neonates needed multiple dose of surfactant proving IDM babies a high risk for surfactant requirement. n 1959 it was first described by Gellis and Hsia that IDMs had increased mortality and morbidity due to RDS [21]. A retrospective analysis by Robert, et al. Showed that after controlling for other confounder factors, IDMs have a 5.6 times greater risk of developing RDS than those infants of nondiabetic gestation [22]

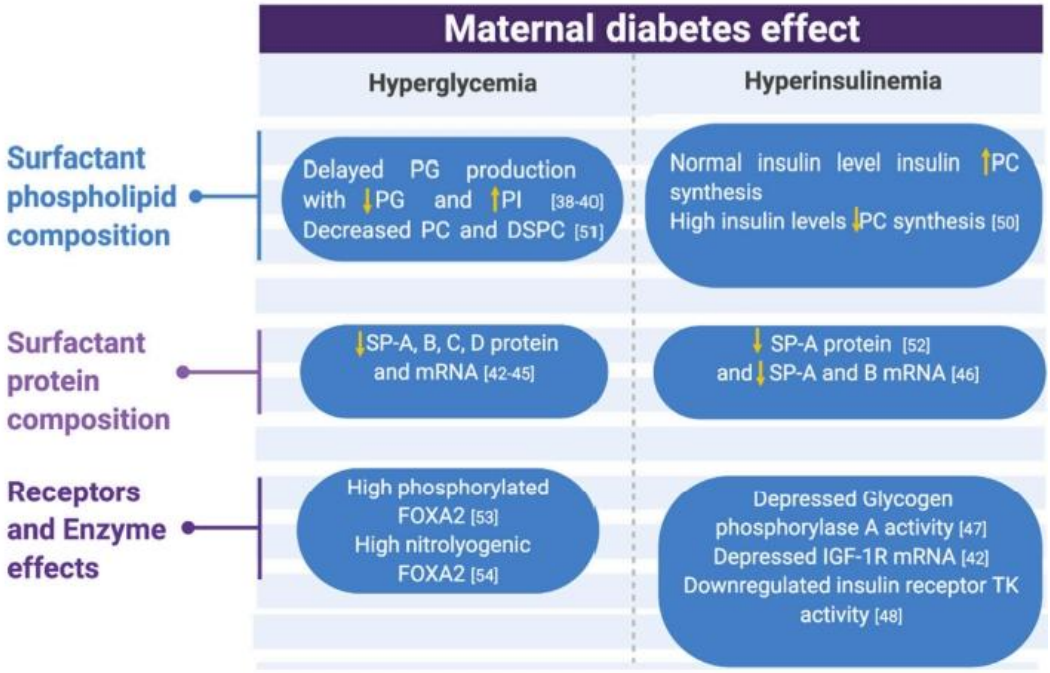

FIG2:PATHOGENESIS OF RDS IN IDM INFANTS

B) Antenatal steroids were found protective for the neonates as only 14% of those who received antenatal steroids were given multiple surfatant and 34.8% only needed single dose against 68% of neonates with RDS without surfactant requirement. Cochrane metaanalysis of 18 randomized trials (23)concluded similar results and showed that antenatal corticosteroid therapy reduces the incidence of RDS, neonatal death and intraventricular haemorrhage. There was evidence of benefit in all major subgroups of preterm babies, regardless of race or gender. Antenatal steroids act on cells called type II pneumocytes and cause both increase rates of cell maturation, as well as increase the production of mRNA coding for proteins required for the surfactant secreted by the lungs in order to increase elasticity and decrease surface tension, consequently generating more efficient rates of ventilation.Another Taiwan based study also showed similar results.

C) Maternal hypertension also seemed to be overall protective with 30% neonates with RDS being managed without any surfactant administration though the corelation in our study was found to be nonsignificant. Other studies conducted by Jelin(24) and Tubman (25)showed that RDS was increased in infants with maternal hypertension. The circulating antiangiogenic factors in mothers with preeclampsia as VEGF ,sflt1, erc are considered to be cause for delayed lung maturity.

3.NATAL FACTORS AND INFLUENCE ON SURFACTANT REQUIREMENT A. Gestation age was found to be one of the most important factors deciding the surfactant requirement($p<0.05$).largest percentage of neonates who received multiple surfactant doses belonged to category of extreme preterm with gestation age 26-28wk(42%) . Also the neonates received at least one dose of surfactant was highest among preterms with 28-32 wk GA (58%). Neonates belonging to 32-36 wk GA was found to have least surfactant requirement(94%). Similar findings were corroborated in mean gestation age of neonates where Overall the mean gestation age requiring multiple surfactant administration was 27 weeks, single surfactant administratiin was 30 wk and no surfectatnt was 34 week.Similar outcomes were seen in two other studies conducted by Stolkhorst et.al and Ventolini et.al where they found. (26-27)

B. LSCS delivered babies had overall less requirement of surfactant with 54% of them belonging to no requirement group, however another section of neonates born by ceaserean section had needed multiple doses of surfactant(42%).However the parameter was not found statistically significant in our study($p>0.05$) . One metanalysis conducted in USA found The results showed that CS, elective CS, and emergency CS increased RDS and surfactant need in preterm neonates(28). The potential mechanism underlying the association between CS and the risk of neonatal RDS is that labour is associated with catecholamine release and a high concentration of catecholamine in newborn infants is conducive to promoting the absorption of lung fluid and increasing the release of surfactants. The skewed observation of the study may be attributed to larger number of emergency cs done for meconium aspiration or pih and also to the application of antenatal steroids to all indicated inborn preterms.

C Very less difference in administration of surfactant was found among outborn and inborn babies.

3.POSTNATAL FACTORS OF NEONATES AND SURFACTANT REQUIREMENT

A. IUGR babies were found to have overall almost equal surfactant requirement as compared to babies with appropriate for gestation age.48% of the IUGR neonates had no surfactant need with one dose given in 51.1% and only 14.2% needed multiple doses. The correlation between IUGR babies and surfectant administration was found statistically significant in our study whereas this remains a topic of debate.McIntire et.al and Spinillo et.al two studies conducted on IUGr preterms and need of surfactant found severe RDS in IuGr more as compared to AGA babies.(29). Several underlying mechanisms have been postulated to explain this increased incidence of RDS in IUGR infants, such as reduced or impaired surfactant release or diminished response to glucocorticoids. *In utero*, IUGR fetuses must adapt to chronic hypoxia to survive. One key adaptation is the redistribution of cardiac output to preferentially provide blood flow and oxygen supply to the brain and heart, commonly referred to as "brain-sparing." It necessitates reduced oxygen supply to other organs during development, including the lungs.(30)

B. Neonates who received active resusctitaion at birth had higher requirement of surfactant requirement(13.9% single and 28.5%multtiple doses). This is correlated mostly perhaps to the extreme preterms and those with severe RDS who went in secondary apnea requiring CPR at birth.

4.0utcome in surfectant received neonates:

Neonates who received multiple doses of surfactant were identified to have increased odds of mortality and major morbidities in a dose-dependent manner. Our subgroup analyses of neonates GA 26–28 weeks' GA 28-32wks confirmed the results. Numerically (not statistically), the odds of adverse outcomes were higher in those 26–28 weeks' GA This may have been due to outcomes being more prevalent in the lower compared to the higher GA group(32); it reinforces point that it is the severity of lung disease that necessitates repeated doses of surfactant.

Among various neonatal morbidities, most of the studies have reported a decrease in the incidence of air leaks with use of prophylactic surfactant(33 34 35 36) however our study could not establish any such correlation. However overall morbidity and mortality was significantly higher in neonates with multiple doses of surfectant which to some extent may be attributable to their extreme prematurity lending them susceptible to need of multiple dose. This has been also established in other studies as well. (37)

Clinical Care after Dosing

Because natural surfactants may work quickly, the clinician must be prepared after dosing to immediately lower the Fio2 while carefully monitoring the pulse oximeter. The tidal volume, as measured by the ventilator and/or by careful observation of chest wall movement, may gradually increase, resulting in a need to lower inspiratory pressures to avoid air leak syndrome, lung injury, and possibly pulmonary hemorrhage. Blood gases should be monitored .PEEP should be maintained but may be reduced given that functional residual capacity increases shortly after surfactant administration.A poor response to exogenous surfactant may occur because the patient does not have surfactant deficiency but rather, lung hypoplasia, pneumonia, or congenital heart disease. Other causes for a lack of response may be poor distribution of the surfactant, such as administration down the right stem bronchus due to malposition of the endotracheal tube, plugging of the tube, or malposition of the tube in the esophagus. A less likely reason is an inadequate dose of surfactant.

The rapid improvement in lung compliance after exogenous surfactant therapy may lead to excessive pulmonary blood flow from left-to-right shunting from a patient ductus arteriosus (Raju and Langerberg, 1993).

V. Conclusion

In conclusion, among infants of <29 weeks' gestation, those who received single or multiple doses of surfactant had higher odds of mortality and major morbidities, including severe brain injury, BPD, and severe retinopathy, than those who did not receive surfactant

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