Winter 1-4-2019

Use of Surfactants for the treatment of Neonatal Respiratory Distress Syndrome

Rajesh V Dr

USE OF SURFACTANTS IN THE TREATMENT OF NEONATAL RESPIRATORY DISTRESS SYNDROME

A Project Report Submitted to

MANIPAL ACADEMY OF HIGHER EDUCATION

In partial fulfillment for the degree of Doctor of Pharmacy (Pharm D)

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Declaration

We hereby declare that the project entitled,

"Use of Surfactants for the treatment of Neonatal Respiratory Distress Syndrome" was carried out under the guidance of **Dr.Rajesh V,** Department of Pharmacy Practice, Manipal College of Pharmaceutical Sciences, Manipal Academy of Higher Education, Manipal and co-guides **Dr. Leslie Edward Lewis,** Unit head Neonatology,KMC, Manipal Academy of Higher Education and **Dr. M.Surulivel Rajan**,Associate professor , Department of Pharmacy Practice, Manipal College of Pharmaceutical Sciences

The extent and source of information derived from the existing literature have been indicated throughout the project work at appropriate places. The work is original and has not been submitted in part or full for any diploma or degree purpose for this or any other university.

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Acknowledgement

"In the name of God, the Almighty, the most Generous and Merciful"

We express our utmost gratefulness to the almighty for the blessing throughout this study.

We are extremely thankful to our parents, teachers and friends for giving us the opportunity to carry ourselves forward in the path of dream and for their unflagging love, care, attention, concern and support throughout our life.

We humbly owe gratitude and sincere regards to our respected guide **Dr. Rajesh V,** Assistant professor, Department of Pharmacy Practice, Manipal College of Pharmaceutical Sciences and our co-guide **Dr. M.Surulivel Rajan ,** Associate professor, Department of Pharmacy Practice, Manipal College of Pharmaceutical Sciences for their valuable guidance, encouragement, untiring patience and support laid by them during all stages of our work. Their encouragement and fruitful suggestions have enabled to make our work worthy of presentation.

We extend our sincere and heartfelt thanks to **Dr. Leslie Edward Lewis,** for his endless support and cooperation.

We would like to thank our departmental non-teaching staff **Mrs. Ashalatha and Mr. Abhilash** for their endless support and cooperation.

Special thanks to the staff of IP MRD, **Kasturba Hospital, Manipal** who have directly or indirectly made us capable for successful completion of the study.

LIST OF ABBREVIATIONS

RDS	Respiratory distress syndrome
DPPC	Dipalmitoylphosphatidylcholine
PROM	Preterm rupture of the membrane
IDM	Infant of Diabetic mother
BPD	Bronchopulmonary dysplasia
NCPAP	Nasal continuous positive airway pressure
ABG	Arterial blood gases
PCo2	Partial pressure of carbon dioxide
PO2	Partial pressure of oxygen
HCO3	Bicarbonate
BE	Base excess

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ABSTRACT

ABSTRACT

Background: Respiratory Distress Syndrome (RDS) is breathing disorder that affects the newborns especially preterm neonates, extremely low birth weight and very low birth weight neonates. This is due to lack of surfactant production in the lungs of a premature baby. Surfactant therapy and oxygen support improves the condition of the neonate with RDS. Use antenatal steroid prevents the occurrence of RDS/reduces the severity of RDS. This study is necessary to assess which surfactant is better, risk factors associated with RDS and comorbidities of neonates present along with RDS.

Objectives: The objectives of the studies are to compare the surfactants used in the treatment of respiratory distress syndrome in neonates, assessing risk factors associated with RDS, to evaluate correlation of RDS with other comorbid conditions, to evaluate use of steroids in pregnant mothers and its effects on Neonatal Respiratory Distress syndrome.

Methodology: A retrospective study was conducted over one year where 610 patients were enrolled based on inclusion and exclusion criteria of the study. Their relevant demographics, etiology, treatment patterns were noted. IBM SPSS version 20 was used for statistical analysis.

Results: A total of 610 patients diagnosed with RDS were included in the study. The mean age of the study population was found to be 31.80±3.161 weeks and the mean birth weight was found to be 1647.28±717.31 grams. The incidence of RDS was higher in males (58.03%), extremely low birth weight and low birth weight babies 8.85% and 47.04% respectively, caesarean section delivery 77.04% along with other risk factors such as preeclampsia, IDM, PROM and presence of complications of prematurity associated with RDS. It was found that Curosurf group required less NCPAP as compared to Survanta and Neosurf ($p=0.010$). Curosurf and Survanta significantly reduced pCO_2 values ($p=0.002$ and $p=0.03$ respectively). There was a significant association between APGAR score and severity of RDS at 1 minute and 5 minutes ($p=0.00$) for both 1 minute and 5 minutes and Gestational age and RDS severity ($p=0.00$). There was a significant association between the use of antental steroids and reduction in neonatal mortality ($p= 0.001$).

Conclusion: Curosurf was found to be better of the three surfactants and the risk of RDS reduced with improving APGAR scores, gestational age and birth weight. Other risk factors contributing towards RDS in neonates were found to be preeclampsia, PROM, IDM and hypothyroidism. Use of antenatal steroid reduced neonatal morbidity associated with RDS.

INTRODUCTION

Respiratory Distress Syndrome (RDS) can be defined as a breathing disorder that affects newborns. This disorder is more common in premature infants whereas in full term infants RDS occurs rarely. (National Institute of Health)
According to the Indian National Neonatal Perinatal Database, incidence of RDS was found to be 1.2%, and an RDS-specific mortality rate was found to be 13.5%, in a population in which 31.4% of infants were born at low birth weight and 14.5% were preterm. (National Neonatal Perinatal Database, 2005)

Preterm neonates have highest incidence of RDS followed by post term and term neonates. Transient tachypnea of the newborn is the most common cause of RDS in neonates followed by infections, meconium aspiration syndrome, hyaline membrane disease and birth asphyxia. Transient tachypnea of newborn was found to be the most common cause among both term and preterm neonates whereas Hyaline membrane disease was mostly seen in preterm neonates, whereas Meconium aspiration syndrome in term and post term babies. (Kumar and Vishnu Bhat, 1996) Among premature babies, the risk of developing RDS was found to be increased among Caucasian race, male sex, and an older sibling with RDS, caesarean delivery, perinatal asphyxia, and maternal diabetes. (Goldenberg et al., 2008).

Lungs of premature infants do not have the ability to make enough surfactant. In the insides of the lungs, surfactant acts like a liquid coat. Which helps keep them open so that infants can breathe in air once they are born. (National Institute of Health). Without enough surfactant, the lungs tend to collapse and the infant has to work hard to breathe. The infant might not be able to breathe in enough oxygen to support the body's organs. If proper treatment is not provided, lack of oxygen can damage the baby's brain and other organs, this in turn leads to increased levels of carbon dioxide in the blood. Most babies who develop RDS exhibit signs of breathing problems and a lack of oxygen at birth or within the first few hours that follow. (National Institute of Health)

The signs and symptoms exhibited by a neonate which includes, respiratory difficulty at birth that progressively worsens, cyanosis, flaring of the nostrils, tachyapnea, grunting sounds while breathing, chest retractions. (National Institute of Health)

Antenatal steroid treatment has emerged to be the most effective intervention for the prevention of RDS in neonates for women who are at risk of preterm delivery, which in turn

helps in reducing early neonatal mortality and morbidity. Most glucocorticoid hormones, whether natural or artificial, are capable of crossing the placenta which trigger the maturational process leading to the production and release of surfactant into the alveoli of the foetal lung (Mwansa – Kambafwile et al., 2010)

The National Institutes of Health (NIH) Consensus Development Conference recommended treatment regimens with either two doses of 12 mg of betamethasone that can be given intramuscularly 24 hours apart or four doses of 6 mg of dexamethasone given intramuscularly 12 hours apart between 24 and 34 weeks of gestation in pregnancies who are at risk for preterm delivery. It is well established that a complete course of antenatal corticosteroids is better than an incomplete course in decreasing the risk of RDS. (Chen et al., 2005).

When optimal prenatal care is provided, the best approach to treat RDS, according to several recent trials, (Subramanian, Ho and Davis, 2016) consists in providing continuous positive airway pressure from the first minutes of life using short binasal prongs, (De Paoli et al., 2008) which is then followed by early selective surfactant administration for babies with worsening of oxygenation and/or increasing work of breathing. Both European and American guidelines advise in favour of this strategy, which reduces mortality and bronchopulmonary dysplasia (BPD). Mechanical ventilation is one of the most common therapies in the neonatal intensive care unit (NICU). (Al Hazzani et al., 2017)

Currently available surfactants are animal-derived preparations. They resulted to be superior to older synthetic (protein-free) surfactants, as the proteins improve surfactant activity, stabilizing the film at the air/liquid interface. (Aedell, Pfister and Soll, 2015). Secretion into the alveolus by type II epithelial cells will lead to synthesis of surfactant lipids and proteins, a process that is developmentally regulated and influenced by hormones like glucocorticoids Jobe and Ikegami (2000). (Whitsett and Stahlman, 2010). Surfactant storing Lamellar bodies appear at 22 to 24 weeks. Surfactant is a mixture of lipids and apoproteins, the main constituents include dipalmitoylphosphatidyl choline(DPPC), phosphatidylglycerol(PG) and apoproteins A, B, C and D. Surfactant maintains stability when breathing out, to prevent collapse of the alveoli. (Roberts et al, 2017).

With increasing gestational age the surfactant production will increase in the normal neonate. Causes of RDS are the lack of lung maturity and surfactant deficiency. Various factors can

inactivate surfactant such as presence of meconium in the airways, pulmonary edema, alveolar capillary leak and pulmonary hemorrhage. Decrease in the activity of a surfactant may result in alveolar collapse, atelectasis, ventilation-perfusion abnormalities, decreased lung compliance, resulting in a decreased ventilation and pulmonary hypertension leading to respiratory failure. Surfactant enhances the clearance of lung liquid and maintaines lung volume. Surfactant replacement decreases the incidence of air leak and mortality that accompany RDS. (Whitsett and Stahlman, 2010)

Commonly used surfactants used for treatment of RDS are; [13]; (Tridente, De Martino and De Luca,2019)

Biochemical Name	**Trade Name**	**Surfactant type**	**Source of extract**	**Total PL (mg/ml)**	**Main PL**	**SP-B (mg/ml)**	**SP-C (mg/ml)**
Beractant	Survanta	Natural	Bovine, minced lung	25	DPPC 70% PS 4%	0.03	0.3
Poractant alpha	Curosurf	Natural	Porcine minced lungs	27	DPPC 42% PG 11%	0.17	0.49
Bovine lipid extract surfactant (BLES)	Neosurf	Natural	Bovine lung lavage	80	DPPC 46% PE 6%	0.45	0.9
DPPC-dipalmitoylphosphatidylcholine; SP-B -Surfactant protein B; SP-C-Surfactant protein C; PL-phospholipids; PS-phosphatidylserine; PG-phosphatidylglycerol; PE-bovine brain phosphatidylethanolamine							

In a Cochrane meta-analysis surfactants were subdivided according to the extraction method (lung lavage or minced lung extract) and into bovine and porcine-derived. The result showed that porcine minced surfactant had more favourable outcomes than those treated with bovine minced lung surfactant. No significant difference between bovine lung lavage and bovine minced lung-derived surfactant were found. (Singh et al., 2015).

NEED FOR STUDY

Need for study:

Respiratory distress syndrome (RDS) is the most common cause of respiratory failure and morbidity and mortality in premature infants. In developing countries, RDS mortality rate and percentage of complications still remain high in comparison to the developed countries, despite facilities for respiratory care of newborn RDS infants requiring Mechanical Ventilation (MV) had survival rate of 25% in the newborns with birth weight <1000 grams up to 53% in those with birth weight >2500 grams. There is limited data about causes of high mortality rate in infants with RDS from developing countries. Outcome of neonatal RDS can be improved by improvement of perinatal care and diminution of risk factors, use of a surfactant as well as antenatal steroids. (Fidanovski et al., 2005)

AIM & OBJECTIVES

Aim:

- To assess, understand and compare the role and use of surfactants used in the prevention and treatment of Respiratory Distress Syndrome in neonates, to interpret the effectiveness and use antenatal steroids in reducing the severity of RDS in neonates, to assess the risk factors and comorbidities associated with Respiratory Distress Syndrome.

Objectives:

- Comparison of surfactants used in the treatment of Respiratory Distress Syndrome in neonates.

- Assessing risk factors associated with Respiratory Distress Syndrome

- To evaluate use of steroids in pregnant mothers and its effects on Neonatal Respiratory Distress syndrome.

METHODOLOGY

Methodology:

Study site: A study conducted in Kasturba Hospital, Manipal

Study design: Single Centered Retrospective Cross sectional Study.

Study period: One year from the date of approval by the Ethics Committee.

Sample size: 610 patients

Ethics Approval

The Institutional Ethics Committee approval was obtained prior to outset of the study (Approval number: 399/2018) (Appendix 1).

Study Criteria

Inclusion criteria: Patients admitted under ICD code P22.0 from the year 2012-2017.

Exclusion criteria: Incomplete data; i.e. when more than 50 per cent of data per patient is unavailable, the data is excluded.

Data source:

The study population broadly represents South Indian population. All the necessary and relevant data were obtained from the medical records of patients diagnosed with Respiratory distress syndrome during the study period.

Materials used: Case Record Form (CRF).

Operation modality:

Patient identification and enrolment: Cases were identified from the MRD by International Classification of Diseases (ICD) code for Neonatal Respiratory Distress Syndrome ICD P 22.0 from the year 2013 to 2017

Collection of data: Patient medical records of all Neonatal Respiratory Distress Syndrome were reviewed and all the required information like demographic details, treatment pattern and outcome of each patient was entered in the CRF.

Statistical Analysis:

For data analysis, Statistical Package for Social Sciences (SPSS) version 20.0 was used. Categorical data was presented as frequencies with percentages. Continuous data was presented as mean ± SD. For the primary objective i.e. Comparison of surfactants used in the treatment of Respiratory Distress Syndrome in Neonates One-way ANOVA and cross tabs with Chi-square were used. Whereas for other objectives i.e assessing the risk factors, comorbidities and use of antenatal steroids various tests such as descriptives with frequency, crosstabs with Chi square and One-way ANOVA were used. A p-value of less than 0.05 was found to be statistically significant.

RESULTS

Patient Characteristics:

A total of 610 patients diagnosed with RDS were included in the study. The mean age of the study population was found to be 31.80±3.161 weeks and the mean birth weight was found to be 1647.28±717.31 grams.

The demographic characteristics of these patients are depicted in the table below:

Table 1: Demographic characteristics of neonates with RDS

Characteristics	Number of Neonates n (%)
Gender	
• **Male**	354 (58.03)
• **Female**	256 (41.96)
Gestational age	
• **Extremely preterm (<28 weeks)**	54 (8.85)
• **Very preterm (28 – 32 weeks)**	287 (47.04)
• **Moderate to late preterm**	240 (39.34)
• **Term**	16 (2.62)
• **Not available**	13 (2.13)
Birth weight	
• **Extremely low birth weight (<1000 g)**	106 (17.37)
• **Very low birth weight (<1500 g)**	186 (30.49)
• **Low birth weight (<2500 g)**	241 (39.50)
• **Normal (2500 – 4500 g)**	67 (10.98)
• **Macrosomia (>4500 g)**	2 (0.32)
• **Not Available**	8 (1.31)
Mode of delivery	
• **Vaginal**	133 (21.80)
• **Caesarean**	470 (77.04)
• **Not available**	7 (1.14)
Multiple pregnancy	
• **Yes**	112 (18.36)
• **No**	498 (81.63)
Preterm rupture of the membrane	
• **Yes**	113 (18.52)
• **No**	497 (81.47)
Preeclampsia	
• **Yes**	121 (19.83)
• **No**	489 (80.16)
Infant of Diabetic mother	
• **Yes**	44 (7.21)
• **No**	566 (92.78)

Table 1: Demographic characteristics of neonates with RDS (contd.)

Antenatal steroid • **No steroid** • **Betamethasone** • **Dexamethasone** • **Both** • **Steroid given but details not known** • **Not available**	 98 (16.06) 32 (5.24) 29 (4.75) 1 (0.16) 202 (33.11) 248 (40.65)
Pneumothorax • **Yes** • **No**	 16 (2.62) 594 (97.37)
Retinopathy • **Yes** • **No**	 89 (14.59) 521 (85.40)
Patent ductus arteriosus • **Yes** • **No**	 42 (6.88) 568 (93.11)
Bronchopulmonary dysplasia • **Yes** • **No**	 2 (0.32) 608 (99.67)
Intracranial haemorrhage • **Yes** • **No**	 6 (0.98) 604 (99.01)
Pulmonary haemorrhage • **Yes** • **No**	 8 (1.31) 602 (98.68)
Ventilator therapy • **Yes** • **No**	 99 (16.22) 511 (83.77)
NCPAP support • **Yes** • **No**	 238 (39.01) 372 (60.98)
NCPAP support + Ventilator therapy • **Yes** • **No**	 235 (38.52) 375 (61.47)
Death • **Yes** • **No** • **Not available**	 58 (9.50) 551 (90.32) 1 (0.16)

According to the table depicted above (Table 1), frequencies of various characteristics that are associated among neonates who were diagnosed with RDS are as follows; out of 610 neonates, 354 (58.03%) neonates were male, 256 (41.96%) neonates were females, 54 (8.85%) neonates were Extremely preterm (<28 weeks), 287 (47.04%) of neonates were Very preterm (28 – 32 weeks), 240 (39.34%) neonates were Moderate to late preterm,16 (2.62%)

neonates were born within the appropriate gestational age and were term babies. With respect to birth weight of neonates; 106 (17.37%) neonates had extremely low birth weight (<1000 g), 186 (30.49%) neonates had very low birth weight (<1500 g), 241 (39.50%) neonates had low birth weight (<2500 g), 67 (10.98%) neonates had normal birth weight (2500 – 4500 g), 2 (0.32%) neonates were found to be Macrosomial (>4500 g). With regard to mode of delivery; 133 (21.80%) neonates were delivered through vaginal delivery and 470 (77.04%) of neonates were delivered by caesarean. 112 (18.36%) of mothers had multiple pregnancies, 113 (18.52%) mothers had preterm rupture of the membrane, 121 (19.83%) mothers had preeclampsia, and 44 (7.21%) neonates were found to be infants of Diabetic mothers. With respect to the mother receiving antenatal steroid; 98 (16.06%) neonates did not receive steroids, 32 (5.24%) mothers received betamethasone, 29 (4.75%) mothers received dexamethasone, 1(0.16%) mother received both betamethasone and dexamethasone, 202 (33.11%) mothers had received steroid but details of which steroid that was received were not known. 16 (2.62%) neonates had pneumothorax, 89 (14.59%) neonates had retinopathy, 42 (6.88%) neonates had patent ductus arteriosus, 2 (0.32%) had bronchopulmonary dysplasia, 6 (0.98%) neonates had intracranial haemorrhage, 8 (1.31%) neonates had pulmonary haemorrhage. 99 (16.22%) neonates received ventilator therapy, 238 (39.01%) had received NCPAP support and 235 (38.52%) neonates had received both NCPAP support and ventilator support. The mortality was found to be 9.50% (58 of 610).

Incidence of RDS over the years:

The incidence of RDS was found to be the highest in the year 2015 followed by 2016,2017 and 2014 respectively.

2013* had more number of cases than depicted but, only 20 were accessible. (Figure 1)

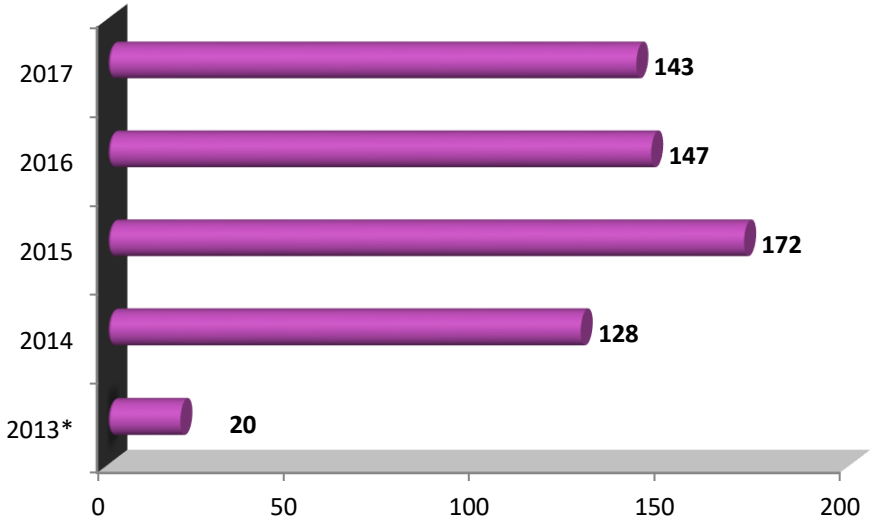

Figure 1: Incidence of RDS over the years

Distribution of Neonates According to RDS Severity

Maximum number of neonates were under the category Mild 240 (39.34) followed by Severe 160 (26.22), Moderate 156 (25.5), Severity not specified 28 (4.59) and Severity not available 26(4.26) respectively. (Figure 2)

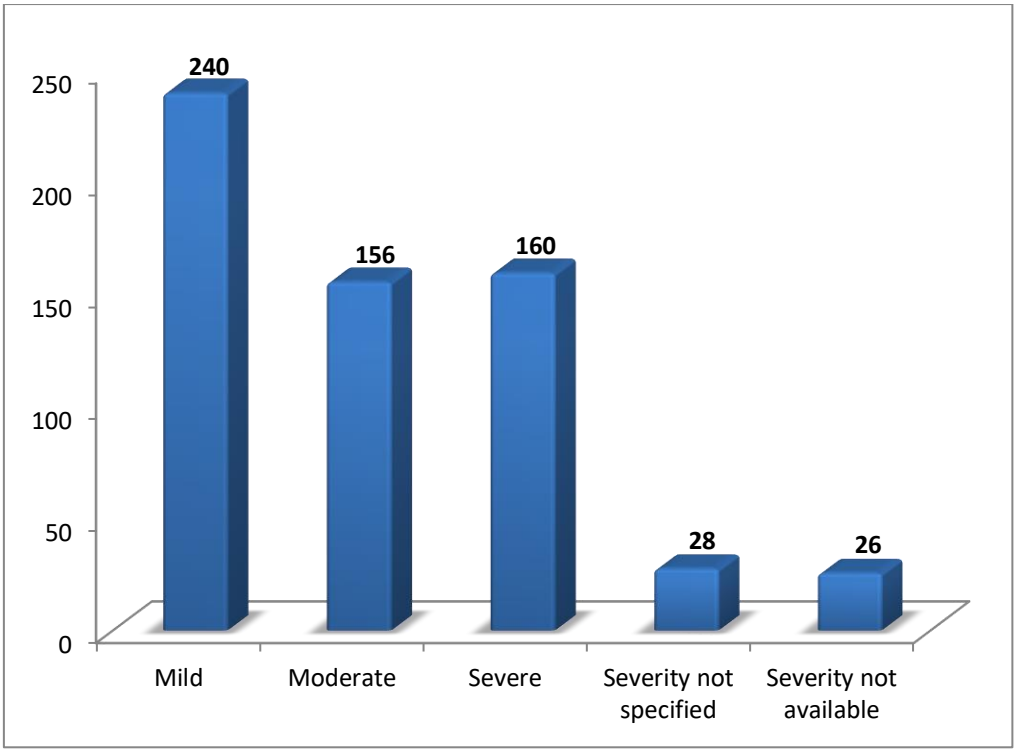

Figure 2: distribution of neonates according to RDS severity

Comparison of Surfactants used in the Treatment of Respiratory Distress Syndrome in Neonates

Out of 610 patients a total of 192 patients were given surfactant.(Figure 3) Out of which 136(70.83) patients were given Survanta followed by Curosurf (21.87), Neosurf (4.68) and one neonate was given both Survanta and Neosurf (0.52) and unknown surfactant 4(2.08). (Figure 4)

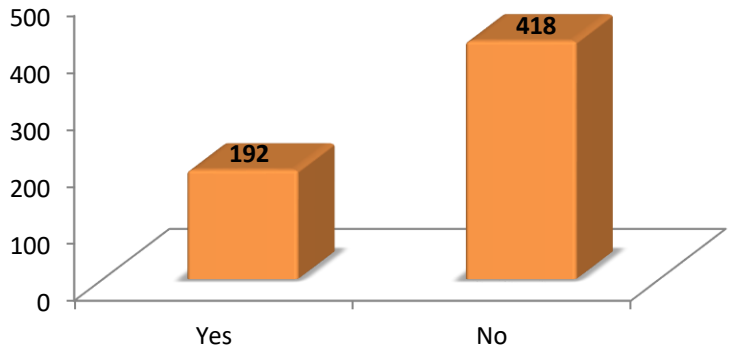

Figure 3: Distribution of neonates according to surfactant treatment

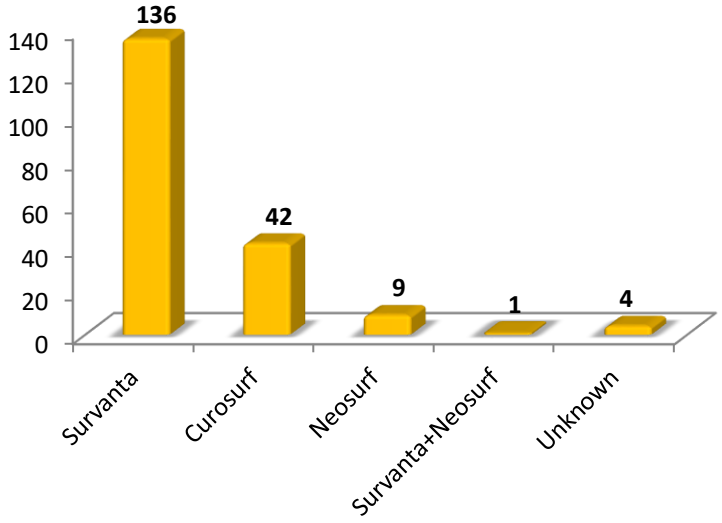

Figure 4: Distribution of neonates as per the type of surfactant given

Table 2: General Characteristics and frequency before intervention

Variables	Type of Surfactant				p Value	Total (%)
	Survanta	Curosurf	Neosurf	Not known		
Gender						
• **Male**	78 (69.64)	24 (21.42)	7 (6.25)	3 (2.67)		112 (58.63)
• **Female**	58 (73.4)	18 (22.78)	2 (2.53)	1 (1.26)	0.587	79 (41.36)
Gestational age (weeks)						163(87.16)
• **≤32**	110(67.48)	41 (25.15)	9(5.52)	3(1.84)	0.017	24(12.83)
• **>32**	23(95.83)	0	0	1(4.16)		
Birth weight (grams)						
• **<1,500**	103 (66.45)	41 (26.45)	9 (5.80)	2 (1.29)		155 (81.15)
• **1,500-2,500**	29 (93.5)	0	0	2 (6.45)		31 (16.23)
• **>2,500**	4 (80)	1 (20)	0	0	0.012	5 (2.61)
Mode of Delivery						
• **Caesarean**	105 (71.91)	30 (20.54)	7 (4.79)	4 (2.73)		146 (76.84)
• **Vaginal**	30 (68.18)	12 (27.27)	2 (4.54)	0	0.881	44 (23.15)
Pneumothorax						
• **Yes**	6 (100)	0	0	0		6 (3.14)
• **No**	130 (70.27)	42 (22.70)	9 (4.86)	4 (2.16)	0.474	185 (96.85)
Sepsis						
• **Yes**	31 (58.49)	18 (33.96)	3 (5.66)	1 (1.88)		53 (27.74)
• **No**	105 (76.08)	24 (17.39)	6 (4.34)	3 (2.17)	0.086	138 (72.25)
Patent Ductus Arteriosus						
• **Yes**	15 (78.94)	3 (15.78)	1 (5.26)	0	0.801	19 (9.94)
• **No**	121 (70.34)	39 (22.67)	8 (4.65)	4 (2.32)		172 (90.05)

Table 2: General Characteristics and frequency before intervention(contd.)

Retinopathy • **Yes** • **No**	32 (74.41) 104 (70.27)	6 (13.95) 36 (24.32)	3 (6.97) 6 (4.05)	2 (4.65) 2 (1.35)	0.256	43 (22.51) 148 (77.48)
Bronchopulmonary Dysplasia • **Yes** • **No**	- 136 (71.20)	- 42 (21.98)	- 9 (4.71)	- 4 (2.09)	-	191 (100)
Intracranial Hemorrhage • **Yes** • **No**	4 (100) 132 (70.58)	0 42 (22.45)	0 9 (4.81)	0 4 (2.13)	0.648	4 (2.09) 187 (97.90)
Pulmonary Hemorrhage • **Yes** • **No**	4 (80) 132 (70.96)	0 42 (22.58)	0 9 (4.83)	1 (20) 3 (1.61)	0.026	5 (2.61) 186 (97.38)
Preeclampsia • **Yes** • **No**	28 (62.22) 108 (73.97)	15 (33.33) 27 (18.49)	1 (2.22) 8 (5.47)	1 (2.22) 3 (2.05)	0.180	45 (23.56) 146 (76.43)
Preterm Rupture of Membrane • **Yes** • **No**	31(73.80) 105(70.46)	8(19.04) 34(22.81)	2(4.76) 7(4.69)	1(2.38) 3(2.01)	0.963	42 (21.9) 149 (78.01)
Infant of Diabetic Mother • **Yes** • **No**	10 (76.92) 126 (70.78)	2 (15.38) 40 (22.47)	1 (7.69) 8 (4.49)	0 4 (2.24)	0.826	13 (6.80) 178 (93.19)

191 of 610 neonates were given Surfactant therapy. The neonates were divided based on the surfactant given and further subdivided on various characteristics such as gender (male/female), gestational age (≤32/>32 weeks) , birth weight (<1,500gm /1,500-2,500gm/ >2,500gm), mode of delivery (vaginal/caesarean), pneumothorax, sepsis, patent ductus arteriosus, retinopathy, bronchopulmonary dysplasia, intracranial hemorrhage, pulmonary hemorrhage, preeclampsia, preterm rupture of the membrane, infant of diabetic mother and death.

Among those variables, the following were found to be statistically significant;
Gestational age (≤32/>32 weeks) (p value=0.017) which signifies there is a difference in the usage of surfactants between the two groups. Surfactants were used more in ≤32 weeks Survanta 110 (67.8), Curosurf 41 (21.15), Neosurf 9 (5.52) and surfactant not known 1 (1.84) whereas in >32 weeks group the use of surfactants was as follows; Survanta 23 (95.83) and surfactant not known 1 (4.16).

Birth weight (p value=0.012) which signifies there is a difference in the usage of surfactants between the three groups. In neonates with weight <1,500 gm the surfactant use was more i.e. Survanta 103 (66.45), Curosurf 41 (26.45), Neosurf 9 (5.80) and surfactant not known 2 (1.29). Survanta 29 (93.5) was used in neonates with weight 1,500gm-2,500gm of body weight. Curosurf and Neosurf were not given in this group, where as surfactant not known in 2 (6.45) cases. In neonates with weight >2,500gm the surfactants use were Survanta 4 (80), Curosurf 1 (20) and Neosurf was not given in this group.

Pulmonary hemorrhage (p value=0.026) the difference between the groups for the incidence rate of pulmonary hemorrhage was statistically significant.

Table 3: Comparison between the effects of the three types of surfactants on different variables among neonates receiving surfactant after intervention

Variable	Type of Surfactant			p Value
	Survanta	Curosurf	Neosurf	
Duration of hospital stay (days) (mean±SD)	33.24±25.187	33.69±25.220	29.33±21.541	0.891
Birth weight (g) (mean±SD)	1306.50±659.63	1080.23±409.58	1105.55±241.31	0.081
Gestational age (weeks) (mean±SD)	29.77±2.820	28.95±1.85	29.11±1.83	0.189
Ventilation time (days) (mean±SD)	13.19±13.894	15.90±15.771	12.22±15.015	0.537
Number of Surfactant injections (mean±SD)	1.06±0.266	1.12±0.395	1±0.00	0.394
Pneumothorax				
• **Yes**	6	0	0	
• **No**	130	42	9	0.313
Patent ductus arteriosus				
• **Yes**	15(78.94)	3(15.78)	1(5.26)	
• **No**	121(72.02)	39(23.21)	8(1.19)	0.763

Table 3: Comparison between the effects of the three types of surfactants on different variables among neonates receiving surfactant after intervention (contd.)

BPD • **Yes** • **No**	- 136(72.72)	- 42(22.45)	- 9(4.81)	-
Intracranial haemorrhage • **Yes** • **No**	4(100) 132(72.13)	0 42(22.95)	0 9(4.91)	0.465
Pulmonary haemorrhage • **Yes** • **No**	4(100) 132(72.13)	0 42(22.95)	0 9(4.91)	0.465
Retinopathy • **Yes** • **No**	32(78.04) 104(71.23)	6(14.63) 36(24.65)	3(7.31) 6(4.10)	0.313
Ventilator therapy • **Yes** • **No**	21(63.63) 115(74.67)	12(27.90) 30(19.48)	0 9(6.08)	0.054
NCPAP support • **Yes** • **No**	9(64.28) 127(73.41)	2(14.28) 40(23.12)	3(21.42) 6(3.46)	0.010
NCPAP support and Ventilator therapy • **Yes** • **No**	104(75.36) 32(65.30)	28(20.28) 14(26.92)	6(4.34) 3(6.12)	0.398

A total of 191 neonates were given surfactant therapy. Neonates who were given surfactant but the name was not known were excluded (4). 187 neonates were then assessed based on their effects on different variables.

p value of 0.010 was found for NCPAP support which indicates that there is a significant difference in the number of neonates requiring NCPAP support. Curosurf group had the least number of neonates (2) who required NCPAP support after intervention.

There were no statistically significant differences between neonates treated with Survanta/Curosurf or Neosurf in terms of other factors mentioned in the table.

In the next section, the neonates whose gestational age was not mentioned and who were given a surfactant but it was not known which were excluded. (A total of 8 neonates were excluded from a total of 191)

Table 4: Effects of different surfactants on various variables among neonates receiving surfactant according to their gestational age- less than or equal to 32 weeks

Variables	Type of Surfactant			p value
	Survanta	Curosurf	Neosurf	
Duration of hospital stay (days) (mean±SD)	37.08±26.007	34.24±25.273	29.33±21.541	0.608
Birth weight (g) (mean±SD)	1172.681±576.400	1027.317±226.680	1105.555±241.317	0.278
Gestational age (weeks) (mean±SD)	28.854±2.106	28.9512±1.856	29.111±1.833	0.916
Ventilation time (days) (mean±SD)	14.45±14.86	16.24±15.81	12.22±15.01	0.708
Sex • **Male** • **Female**	 63 (67.02) 47 (71.21)	 24 (25.53) 17 (25.75)	 7 (7.44) 2 (3.03)	 0.486
Pneumothorax • **Yes** • **No**	 2 (100) 108 (68.35)	 0 41 (25.94)	 0 9 (5.69)	 0.631
Patent ductus arteriosus • **Yes** • **No**	 7 (63.63) 103 (69.12)	 3 (27.27) 38 (25.50)	 1 (9.09) 8 (5.36)	 0.857
BPD • **Yes** • **No**	 - 110 (68.75)	 - 41 (25.62)	 - 9 (5.62)	-

Table 4: Effects of different surfactants on various variables among neonates receiving surfactant according to their gestational age- less than or equal to 32 weeks (contd.)

Intracranial haemorrhage • **Yes** • **No**	4 (100) 106 (67.94)	0 41 (26.28)	0 9 (5.76)	0.394
Pulmonary haemorrhage • **Yes** • **No**	3 (100) 107 (68.15)	0 41 (26.11)	0 9 (5.73)	0.499
Retinopathy • **Yes** • **No**	31 (77.5) 79 (65.83)	6 (15) 35 (29.16)	3 (7.5) 6 (5)	0.194
Ventilator therapy • **Yes** • **No**	13(54.16) 97(71.32)	11(45.83) 30 (22.05)	0 9(6.61)	0.031
NCPAP support • **Yes** • **No**	7 (58.33) 103 (69.59)	2(16.66) 39(26.35)	3(25) 6(4.05)	0.010
NCPAP support and Ventilator therapy • **Yes** • **No**	88(72.13) 22(57.89)	28 (22.95) 13 (34.21)	6 (4.91) 3 (7.89)	0.254
Death • **Yes** • **No**	19 (61.29) 91 (70.54)	10 (32.25) 31 (24.03)	2 (6.45) 7 (5.42)	0.601

The p values were calculated in the age group of ≤32 weeks a total of 160 neonates were present in this category. Neonates whose age and the name of surfactant was not available were excluded.

p value of 0.010 was found for NCPAP support which indicates that there is a significant difference in the number of neonates requiring NCPAP support. Curosurf group had the least number of neonates; 2 (16.66) who required NCPAP support after intervention as compared to Survanta 7 (58.33) and Neosurf 3 (25).

Table 5: Effects of different surfactants on various variables among neonates receiving surfactant according to their gestational age - more than 32 weeks

VARIABLE	TYPE OF SURFACTANT			p Value
	Survanta	Curosurf	Neosurf	
Duration of hospital stay(days) (mean±SD)	17.48±12.15	-	-	-
Birth weight (g) (mean±SD)	233.74±164.99	-	-	-
Gestational age (weeks) (mean±SD)	34±1.154	-	-	-
Ventilation time (days) (mean±SD)	7.78±6.755	-	-	-
Sex				
• **Male**	13	-	-	
• **Female**	10	-	-	-
Pneumothorax				
• **Yes**	4	-	-	
• **No**	19	-	-	-
Patent ductus arteriosus				
• **Yes**	8	-	-	
• **No**	15	-	-	-
BPD				-
• **Yes**	-	-	-	
• **No**	23	-	-	
Intracranial haemorrhage				
• **Yes**	-	-	-	
• **No**	23	-	-	-
Pulmonary haemorrhage				
• **Yes**	-	-	-	
• **No**	23	-	-	-
Retinopathy				-
• **Yes**	1	-	-	
• **No**	22	-	-	
Ventilator therapy				-
• **Yes**	6	-	-	
• **No**	17	-	-	
NCPAP support				-
• **Yes**	2	-	-	
• **No**	21	-	-	
NCPAP support and Ventilator therapy				-
• **Yes**	15	-	-	
• **No**	8	-	-	
Death				-
• **Yes**	3	-	-	

• **No**	19	-	-	

In the age group of >32 weeks only Survanta was used and therefore p value could not be calculated.

Table 6: Two-by-Two Comparison of the Effects of Survanta and Curosurf on Several Variables among Neonates after Intervention

Variable	Type of surfactant		p Value
	Survanta	Curosurf	
Pneumothorax			
• **Yes**	6 (100)	0	
• **No**	130 (75.58)	42 (24.4)	0.166
Patent ductus arteriosus			
• **Yes**	15 (83.33)	3 (16.66)	
• **No**	121 (75.62)	39 (24.37)	0.465
BPD			
• **Yes**	-	-	
• **No**	136 (76.4)	42 (24.41)	-
Intracranial haemorrhage			
• **Yes**	4 (100)	0	
• **No**	132 (75.86)	42 (24.13)	0.261
Pulmonary haemorrhage			
• **Yes**	4 (100)	0	
• **No**	132 (75.86)	42 (24.13)	0.261
Retinopathy			
• **Yes**	32 (84.21)	6 (15.78)	
• **No**	104 (74.28)	36 (25.71)	0.201
Ventilator therapy			
• **Yes**	21 (63.63)	12 (36.36)	
• **No**	115 (79.31)	30 (20.61)	0.056
NCPAP support			
• **Yes**	9 (81.81)	2 (18.18)	
• **No**	127 (76.04)	40 (23.95)	0.662
NCPAP support and Ventilator therapy			
• **Yes**	104 (78.78)	28 (21.21)	
• **No**	32 (69.56)	14 (30.43)	0.205

No significant difference was found between the Survanta and Curosurf group.

Table 7: Two-by-Two Comparison of the Effects of Survanta and Neosurf on Several Variables among Neonates after Intervention

Variable	Type of surfactant		p Value
	Survanta	Neosurf	
Pneumothorax			
• **Yes**	6 (100)	0	
• **No**	130 (93.52)	9 (6.47)	0.520
Patent ductus arteriosus			
• **Yes**	15 (93.75)	1 (6.25)	
• **No**	121 (93.79)	8 (6.20)	0.994
BPD			
• **Yes**	-	-	
• **No**	136 (93.79)	9 (6.20)	-
Intracranial haemorrhage			
• **Yes**	4 (100)	0	
• **No**	132 (93.61)	9 (6.38)	0.602
Pulmonary haemorrhage			
• **Yes**	4 (100)	0	
• **No**	132 (93.61)	9 (6.38)	0.602
Retinopathy			
• **Yes**	32 (91.42)	3 (8.57)	
• **No**	104 (94.54)	6 (5.45)	0.506
Ventilator therapy			
• **Yes**	21 (100)	0	
• **No**	115 (92.74)	9 (7.25)	0.202
NCPAP support			
• **Yes**	9 (75)	3 (25)	
• **No**	127 (95.48)	6 (4.51)	0.005
NCPAP support and Ventilator therapy			
• **Yes**	104 (94.54)	6 (5.45)	
• **No**	32 (91.42)	3 (8.57)	0.506

A statistically significant difference was found between Survanta and Neosurf group with a p value of 0.005 for NCPAP support. This signifies that Neonates in the Neosurf group required less NCPAP support. No significance was found between other variables.

Table 8: Two-by-Two Comparison of the Effects of Curosurf and Neosurf on Several Variables among Neonates after Intervention

Variable	Type of Surfactant		p Value
	Curosurf	Neosurf	
Pneumothorax			
• **Yes**	-	-	-
• **No**	42 (82.35)	9 (17.64)	
Patent ductus arteriosus			
• **Yes**	3 (75)	1 (25)	
• **No**	39 (82.97)	8 (17.02)	0.688
BPD			
• **Yes**	-	-	-
• **No**	42 (82.35)	9 (17.64)	
Intracranial haemorrhage			
• **Yes**	-	-	-
• **No**	42 (82.35)	9 (17.64)	
Pulmonary haemorrhage			
• **Yes**	-	-	-
• **No**	42 (82.35)	9 (17.64)	
Retinopathy			
• **Yes**	6 (66.66)	3 (33.33)	
• **No**	36 (85.71)	6 (14.28)	0.174
Ventilator therapy			
• **Yes**	12 (100)	0	
• **No**	30 (76.92)	9 (23.07)	0.06
NCPAP support			
• **Yes**	2 (40)	3 (60)	
• **No**	40 (86.95)	6 (13.04)	0.009
NCPAP support and Ventilator therapy			
• **Yes**	28 (82.35)	6 (17.64)	
• **No**	14 (82.35)	3 (17.64)	1.000

A statistically significant difference was found between Curosurf and Neosurf group with a p value of 0.005 for NCPAP support. This signifies that Neonates in the Curosurf group required less NCPAP support. No significance was found between other variables.(Table 8)

Table 9: Comparison of pre and post pH values of the Surfactants used in the treatment of RDS

pH	Survanta (mean±SD)	P value	Curosurf (mean±SD)	P value	Neosurf (mean±SD)	p value
Pre	7±0.000		6.89±0.333		7.25±0.500	
Post	7.03±0.174	**0.325**	7±0.000	**0.347**	7±0.000	**0.391**

There were no significant changes in the pre and post pH values of the three surfactants.

Table 10: Comparison of pre and post pCO2 values of the Surfactants used in the treatment of RDS

pCO2	SURVANTA (mean±SD)	P value	CUROSURF (mean±SD)	P value	NEOSURF (mean±SD)	p value
Pre	52.33±15.793	**0.003**	49.56±11.282	**0.002**	54.50±18.628	**0.466**
Post	41.30±10.853		30.89±8.268		41.50±13.723	

There was a statistically significant difference in pre and post values of pCO2 which is seen in Survanta (p=0.003) and Curosurf (p=0.002) groups. (Table 10)

Table 11: Comparison of pre and post pO2 values of the Surfactants used in the treatment of RDS

pO2	SURVANTA (mean±SD)	p value	CUROSURF (mean±SD)	p value	NEOSURF (mean±SD)	p value
Pre	51.45±37.340	**0.059**	45±28.325	**0.120**	40±29.292	**0.492**
Post	71.27±45.002		57±34.838		64.75±52.506	

There were no significant changes in the pre and post pO2 values of the three surfactants. (Table 11)

Table 12: Comparison of pre and post HCO3 values of the Surfactants used in the treatment of RDS

HCO3	Survanta (mean±SD)	p value	Curosurf (mean±SD)	p value	Neosurf (mean±SD)	p value
Pre	18.75±7.844		12.80±6.380		21±2.646	
Post	20.64±4.165	**0.264**	16.60±1.939	**0.369**	20.33±3.512	**0.868**

There were no significant changes in the pre and post HCO3 values of the three surfactants.(Table 12)

Table 13: Comparison of pre and post BE values of the Surfactants used in the treatment of RDS

BE	SURVANTA (mean±SD)	p value	CUROSURF (mean±SD)	p value	NEOSURF (mean±SD)	p value
Pre	-7.31±4.222		-11.50±3.937		-5.67±3.215	
Post	-4.58±4.300	**0.007**	-8.17±5.636	**0.233**	-7.00±3.464	**0.739**

There was a statistically significant difference in pre and post values of BE in the Survanta group with a p value of 0.007. (Table 13)

ASSESSING RISK FACTORS ASSOCIATED WITH RESPIRATORY DISTRESS SYNDROME

Table 14:Severity of RDS with respect to mothers comorbidities during the gestation period

VARIABLES	SEVERITY OF RDS N (%)		
	MILD	MODERATE	SEVERE
Urinary Tract Infection	5 (7.35)	2 (5.12)	5 (9.09)
Upper Respiratory Tract Infection	1 (1.47)	1 (2.56)	-
Hypertension	38 (55.88)	25 (64.1)	36 (65.45)
Hypothyroidism	10 (14.70)	6 (15.38)	6 (10.90)
Type 2 Diabetes Mellitus	1 (1.47)	1 (2.56)	3 (5.45)
Gestational Diabetes Mellitus	4 (5.88)	2 (5.12)	1 (1.81)
Seizures	5 (7.35)	1 (2.56)	-
Convulsions	2 (2.94)	1 (2.56)	1 (1.81)
Anemia	-	-	1 (1.81)
Hyperthyroidism	2 (2.94)	-	1 (1.81)
Sepsis	-	-	1 (1.81)

The frequencies of results depicted from the table above, it was ascertained that among neonates diagnosed with mild rds the common comorbidities in mothers during that gestation period included urinary tract infection 5 (7.35%), upper respiratory tract infection 1 (1.47%), hypertension 38 (55.88%), hypothyroidism 10 (14.70%), type 2 diabetes mellitus 1 (1.47%), gestational diabetes mellitus 4 (5.88%), seizures 5 (7.35%), convulsions 2 (2.94%) and hyperthyroidism 2 (2.94 %).

Among neonates that had moderate rds, the most common comorbidities among mothers during that gestation period were urinary tract infection 2 (5.12%), upper respiratory tract infection 1 (2.56%), hypertension 25 (64.1%), hypothyroidism 6 (15.38%), type 2 diabetes mellitus 1 (2.56%), gestational diabetes mellitus 2 (5.12%), seizures 1 (2.56%) and convulsions 1 (2.56%).

Among neonates that had severe rds, the most common comorbidities among mothers during that gestation period were urinary tract infection 5 (9.09%), hypertension 36 (65.45%), hypothyroidism 6 (10.90%), type 2 diabetes mellitus 3 (5.45%), gestational diabetes mellitus 1 (1.81%), convulsions 1 (1.81%), anemia 1 (1.81%), hyperthyroidism 1 (1.81%) and sepsis 1 (1.81%).

Table 15: Severity of RDS with respect to medications taken by the mother during the gestation period

VARIABLES	SEVERITY OF RDS N (%)		
	MILD	MODERATE	SEVERE
TT Prophylaxis	174 (37.82)	115 (38.9)	102 (36.29)
Fe/Ca/Folic acid prophylaxis	178 (38.69)	115 (38.9)	104 (37.01)
Neuroprophylaxis	5 (1.08)	3 (1.01)	8 (2.84)
Progesterone	9 (1.95)	6 (2.033)	6 (2.13)
Estrogen	1 (0.21)	1 (0.33)	2 (0.71)
Dydrogesterone	5 (1.08)	3 (1.01)	3 (1.06)
Iron	4 (0.86)	-	2 (0.71)
Nifedipine	5 (1.08)	1 (0.33)	3 (1.06)
Nicardipine	6 (1.30)	3 (1.01)	5 (1.77)
Methyldopa	6 (1.30)	6 (2.03)	5 (1.77)

Table 15: Severity of RDS with respect to medications taken by the mother during the gestation period

Labetalol	15 (3.26)	9 (3.05)	8 (2.84)
Alphadopa	3 (0.65)	-	4 (2.84)
Amlodipine	3 (0.65)	1 (0.33)	3 (1.06)
Aspirin	15 (3.26)	10 (3.38)	10 (3.55)
Ampicillin	1 (0.21)	-	-
Amoxicillin	-	-	1(0.35)
Levothyroxine	9 (1.95)	8 (2.71)	9(3.20)
Magnesium sulphate	7 (1.52)	5 (1.69)	2(0.711)
Metformin	7 (1.52)	4 (1.35)	1(0.35)
Insulin	7 (1.52)	5 (1.69)	3(1.06)

As depicted from the above table, neonates were grouped accordingly based on severity of rds with respect to medications taken by the mother during the gestation period.

Among the neonates who had mild rds, following were the drugs taken during the gestation period; tt prophylaxis 174 (37.82) , fe/ca/folic acid prophylaxis 178 (38.69%), neuroprophylaxis 5 (1.08%), progesterone 9 (1.95%), estrogen 1 (0.21%), dydrogesterone 5 (1.08%), iron 4 (0.86%), nifedipine 5 (1.08%), nicardipine 6 (1.30%), methyldopa 6 (1.30%), labetalol 15 (3.26%), alphadopa 3 (0.65%), amlodipine 3 (0.65%), aspirin 15 (3.26%), ampicillin 1 (0.21%), levothyroxine 9(1.95%), magnesium sulphate 7(1.52%), metformin 7(1.52%) and insulin 7(1.52%).

Among the neonates who had moderate rds, following were the drugs taken during the gestation period; tt prophylaxis 115 (38.9), fe/ca/folic acid prophylaxis 115 (38.9) ,neuroprophylaxis 3 (1.01), progesterone 6 (2.033), estrogen 1 (0.33), dydrogesterone 3 (1.01), nifedipine 1 (0.33) , nicardipine 3 (1.01) , methyldopa 6 (2.03), labetalol 9 (3.05) , amlodipine 1 (0.33), aspirin 10 (3.38), levothyroxine 8 (2.71) , magnesium sulphate 5 (1.69) , metformin 4 (1.35) and insulin 5 (1.69) .

Among the neonates who had severe rds, following were the drugs taken during the gestation period; tt prophylaxis 102 (36.29%), fe/ca/folic acid prophylaxis 104 (37.01%), neuroprophylaxis 8 (2.84%), progesterone 6 (2.13%), estrogen 2 (0.71%), dydrogesterone 3 (1.06%), iron 2 (0.71%) nifedipine 3 (1.06%), nicardipine 5 (1.77%), methyldopa 5 (1.77%), labetalol 8 (2.84%), alphadopa 4 (2.84%), amlodipine 3 (1.06%), aspirin 10 (3.55%), amoxicillin 1(0.35%), levothyroxine 9 (3.20%), magnesium sulphate 2 (0.711%), metformin 1 (0.35%) and insulin 3 (1.06%). (table 15)

Table 16: Severity of RDS with respect to the APGAR score of the neonate

APGAR SCORE	SEVERITY OF RDS			p Value
	MILD	MODERATE	SEVERE	
APGAR 1 MIN (mean±SD)	7.88±1.652	7.38±1.863	7.38±1.863	0.000
APGAR 5 MIN (mean±SD)	8.77±0.648	8.73±0.620	7.5±1.768	0.000

A p value of 0.000 was found for APGAR 1 minute which indicates that there is a significant difference between the mild, moderate and severe groups. In mild RDS, the APGAR score was found to be higher (7.88±1.652) than moderate RDS (7.38±1.863) and moderate RDS had a higher score when compared with severe RDS (7.38±1.863).

A p value of 0.000 was found for APGAR 5 minute which indicates that there is a significant difference between the mild, moderate and severe groups. In mild RDS, the APGAR score was found to be higher (8.77±0.648) than moderate RDS (8.73±0.620) and moderate RDS had a higher score when compared with severe RDS (7.5±1.768) (Table 16)

Table 17: Severity of RDS with respect to Multiple pregnancy, Preterm rupture of membrane and mode of delivery

VARIABLE	SEVERITY OF RDS N(%)		
	MILD	MODERATE	SEVERE
Multiple pregnancy	44 (43.13)	28 (27.45)	30 (29.41)
Preterm rupture of membrane	45 (42.45)	30 (28.30)	31 (29.24)
Mode of delivery			
• **Vaginal**	42 (35.59)	34 (28.81)	42 (35.59)
• **Caesarean**	196 (45.26)	122 (28.17)	115 (26.55)

In association with severity of RDS with respect to mothers who have had multiple pregnancies, it was observed that (43.13%) neonates had mild RDS, (27.45%) neonates had moderate RDS and (29.41%) neonates had diagnosed with severe RDS.

Among mothers who have had preterm rupture of membrane at the time of delivery, it was found that (42.45%) neonates had mild RDS, (28.30%) neonates had moderate RDS and (29.24%) neonates had severe RDS.

With respect to mode of delivery in relation with severity of RDS, it was seen that (35.59%) neonates had mild RDS, (28.81%) of neonates had moderate RDS and (35.59%) neonates were had severe RDS when the mother had delivered the baby vaginally. Among mothers who underwent Caesarean, it was observed that (45.26%) neonates had mild RDS, (28.17%) neonates had moderate RDS and (26.55%) of neonates had severe RDS.

Table 18: Severity of RDS with respect to the Gestational age of the neonate

GESTATIONAL AGE	SEVERITY OF RDS N (%)			p Value
	MILD	MODERATE	SEVERE	
≤32 weeks	88 (28.57)	91 (10.06)	129 (41.88)	0.000
>32 weeks	149 (63.13)	63 (26.69)	24 (10.16)	

Among neonates with gestational age ≤32 weeks, it was found that 88 (28.57%) neonates had mild RDS, 91 (10.06%) neonates had moderate RDS, and 129 (41.88%) neonates had severe RDS. Among neonates with gestational age >32 weeks, it was observed that 149 (63.13%) neonates had mild RDS, 63 (26.69%) neonates had moderate RDS and 24 (10.16%) neonates were had severe RDS.(Table 18)

Table 19: Severity of RDS with respect to the gender of the neonate

GENDER	SEVERITY OF RDS N (%)		
	MILD	MODERATE	SEVERE
Male	138 (42.33)	92 (28.22)	96 (29.44)
Female	102 (44.34)	64 (27.82)	64 (27.82)

Among neonates of male gender, it was seen that 138 (42.33%) neonates had mild RDS, 92 (28.22%) neonates had moderate RDS and 96 (29.44%) neonates had severe RDS. Among neonates of female gender, 102 (44.34%) neonates had mild RDS, 64 (27.82%) neonates had moderate RDS and 64 (27.82%) neonates had severe RDS. (Table 19)

TO EVALUATE RELATION OF RESPIRATORY DISTRESS SYNDROME WITH OTHER COMORBID CONDITIONS.

Table 20: Severity of RDS with respect to comorbidities of the neonate

COMORBIDITIES	SEVERITY OF RDS N (%)		
	MILD	MODERATE	SEVERE
Perinatal asphyxia	-	2 (2.56)	11 (9.73)
Septic shock	1 (1.03)	2 (2.56)	7 (6.19)
Meconium Aspiration Syndrome	-	-	1 (0.88)
Necrotizing Enterocolitis	3 (3.09)	2 (2.56)	4 (3.53)
Acidosis	-	1 (1.28)	5 (4.42)
Pneumonia	4 (4.12)	1 (1.28)	6 (5.30)
Meningitis	4 (4.12)	3 (3.84)	4 (3.53)
Anemia of prematurity	7 (7.21)	8 (10.25)	15 (13.27)
Apnea of prematurity	8 (8.24)	6 (7.69)	2 (1.76)
Neonatal hyperbilirubinemia	45 (46.39)	24 (30.76)	18 (15.92)
Sepsis	25 (25.77)	29 (37.17)	40 (35.39)

The comorbidities associated in respiratory distress syndrome among neonates were compared with respect to severity of rds. Among the neonates who were diagnosed with rds, the most common comorbidities were found to be as follows;

Comorbidities among neonates diagnosed with mild rds were found to be septic shock 1 (1.03%), necrotizing enterocolitis 3 (3.09%), pneumonia 4 (4.12%), meningitis 4 (4.12%), anemia of prematurity 7 (7.21%), apnea of prematurity 8 (8.24%), neonatal hyperbilirubinemia 45 (46.39%) and sepsis 25 (25.77%).

Comorbidities among neonates diagnosed with moderate rds were found to be perinatal asphyxia 2 (2.56%), septic shock 2 (2.56%), necrotizing enterocolitis 2 (2.56%), acidosis 1 (1.28%), pneumonia 1 (1.28%), meningitis 3 (3.84%), anemia of prematurity 8 (10.25%), apnea of prematurity 6 (7.69%), neonatal hyperbilirubinemia 24 (30.76%) and sepsis 29 (37.17%).

Comorbidities among neonates diagnosed with severe rds were found to be perinatal asphyxia 11 (9.73%), septic shock 7 (6.19%), meconium aspiration syndrome 1 (0.88%), necrotizing enterocolitis 4 (3.53%), acidosis 5 (4.42%), pneumonia 6 (5.30%), meningitis 4 (3.53%), anemia of prematurity 15 (13.27%), apnea of prematurity 2 (1.76%), neonatal hyperbilirubinemia 18 (15.92%) and sepsis 40 (35.39%).(table 20)

TO EVALUATE USE OF STEROIDS IN PREGNANT MOTHERS AND ITS EFFECTS ON NEONATAL RESPIRATORY DISTRESS SYNDROME.

Table 21: Severity of RDS with respect to use of antenatal steroids

STEROID	SEVERITY OF RDS N (%)		
	MILD	MODERATE	SEVERE
Yes	111 (46.25)	56 (23.33)	73 (30.41)
No	42 (47.19)	23 (25.84)	24 (26.96)

With respect to use of antenatal steroids and severity of RDS as depicted from table 2, it was revealed that when mothers were given with antenatal steroids, more number of neonates had mild (46.25%) RDS and moderate (23.33%) RDS compared to severe RDS. Hence from this study we can say that use of antenatal steroids can help reduce the severity of RDS in neonates. (Table 21)

Table 22: Relation between use of antenatal steroids and death in neonates

STEROID	DEATH N (%)		P Value
	Yes	No	
Yes	16 (6.299)	238 (93.70)	0.001
No	17 (18.68)	74 (81.31)	

With respect to understanding the relationship between use of antenatal steroids and occurrence of death among neonates diagnosed with RDS; it was observed that 93.70% neonates had improved after the mother had received antenatal steroids while only 81.31% of neonates improved when no steroid was given. Mortality rate was found to be 6.299% in neonates who received antenatal steroids whereas it was 18.68% in neonates who did not receive antenatal steroids; this reveals that use of antenatal steroids reduced the mortality among neonates diagnosed with RDS. (Table 22)

Table 23: Relation between antenatal use of Dexamethasone and death in neonates

Dexamethasone	DEATH N (%)	
	Yes	No
Yes	1 (3.12)	31 (96.87)
No	57 (9.87)	520 (90.12)

From the study, we could observe that when mothers had received antenatal Dexamethasone, reduction of RDS was found to seen among 96.87% of neonates whereas 90.12% of neonates improved when mothers did not receive dexamethasone. Mortality rate was found to be 3.12% when mothers received dexamethasone while mortality rate was found to be 9.87% when mothers did not receive dexamethasone. (Table 23)

Table 24: Relation between antenatal use of Betamethasone and death in neonates

Betamethasone	DEATH N (%)	
	Yes	No
Yes	1 (3.44)	28 (96.55)
No	57 (9.82)	523 (90.17)

From the study, we could observe that when mothers had received antenatal Betamethasone, reduction of RDS was found to seen among 96.55% of neonates whereas 90.17% neonates improved when mothers did not receive betamethasone. 3.44 % of neonates had been succumbed to death when betamethasone was received by the mother while 9.82% of neonates succumbed to death when mothers had not received betamethasone. (Table 24)

DISCUSSION

A retrospective study was carried out at Kasturba Hospital, Manipal in patients with RDS to evaluate the use of surfactants in the treatment of RDS, assess the risk factors and comorbidities associated with RDS and to evaluate the use of antenatal steroids and its effect on RDS in neonates.

The mean gestational age of the study population was 31.80±3.161 week which was similar to a study conducted by Mussavi M et al. where the mean gestational age was 31.6±3.7 weeks. (Mussavi, Mirnia and Asadollahi, 2016). In another study carried out by Bita Najafian et al. the mean gestational age was 32.59±3.39 weeks. (Najafian et al., 2016).

The mean birth weight of the study population was found to be 1647.28±717.31 gram which was similar to a study conducted by Mussavi M et al. where the mean birth weight was 1840±790 grams (Mussavi, Mirnia and Asadollahi, 2016). In another study carried out by Bita Najafian et al. the mean birth weight was 1911.3±786.5 grams. (Najafian et al., 2016).

In our study the highest number of cases was found to be in males which were similar to various studies conducted it was found that males were at an increased risk of RDS for all gestational age while females were said be consistently at lower risk of RDS. (Anadkat et al., 2012)(Melamed et al., 2009)(Yee,Amin and Wood,2008) (Dudell and Jain, 2006) According to another study done by Rubaltelli et al. the male to female ratio of RDS affected infants was found to be 1.3:1. Among the affected newborns, it was found that the case fatality rate (CFR) for respiratory disorders was seen to be higher in males than in females. (Rubaltelli et al., 1998).

We found that frequency of RDS was higher in extremely preterm (47.04%) and very preterm (39.34%) neonates, this is in consistence with study performed by Ghartey et al. who concluded that infants delivered at early term had a two – fold increased risk of RDS, oxygen use, CPAP use and composite respiratory morbidity. (Ghartey et al., 2012)

Neonates with extremely low birth weight and very low birth weight had higher incidence of RDS this was similar to the results of a study conducted by Fehlmann et al. which concluded that incidence of RDS was more in preterm infants of very low birth weight..(Fehlmann et al.,2010)

With regard to mode of delivery we found that incidence of RDS was higher in Caesarean mode of delivery(77.04) this was in agreement with many studies that were carried out had consistently shown that babies born by caesarean section were found to be at a higher risk of developing RDS, this was because neonates born by caesarean section had larger residual volume of lung fluid thereby less surfactant is secreted to the alveolar surface which delayed the clearance of lung fluid .(Anadkat et al., 2012)(Sun et al.,2013)(Hansen et al., 2007) (Ramachandrappa, A. and Jain, L., 2008) and according to Melamed et al. who found a two - fold increased risk of RDS among neonates born by caesarean section. (Melamed et al., 2009).

Our study showed that neonates whose mothers have had multiple pregnancies were at the risk of developing RDS. This result was in consistence with study conducted by Sun et al. which concluded that in both preterm and term infants, multiple gestations were associated with increased risk of RDS. (Sun et al., 2013)

There was an increased risk of developing RDS when the mother was had PROM this was in consistence with the study conducted by Jahromi et al. in which it was found that out of 94 neonates who had preterm rupture of membrane less than 12 hours, 41 cases (43.6%) had developed RDS. Duration of rupture of the membrane among 19 neonates was found to be between 12 and 24h among which 6 of them (31.6%) had developed RDS. In 21 cases whose rupture of the membrane was found to be between 24 to 48 h, RDS was seen among 4 (19%) cases and therefore it was concluded that increase in the duration of preterm rupture of the membrane in the first 48 hours decreased the risk of RDS with a linear pattern. (Namavar Jahromi, Ardekany and Poorarian, 2000).

Our study concluded that mothers who had preeclampsia and diabetes during gestation led to an increased risk of neonates developing RDS which was reciprocal to the study conducted by Pugni et al. in which it was found that all infants small for gestational age prematurely born from preeclamptic women, appeared to be a high risk group for adverse respiratory

outcome (Pugni et al.,1999) and according to the study conducted by Piper et al. it was concluded that pregnancies in which maternal glucose levels were found to be poorly controlled, there was an association with delayed appearance of biochemical indicators of pulmonary maturity such a phosphatidylglycerol.(Piper, Xenakis and Langer, 1998).
Various complications of prematurity were elated to RDS such as pneumothorax, retinopathy, patent ductus arteriosus, BPD, intracranial hemorrhage and pulmonary hemorrhage which was similar to the result of a study done by Agrons et al. various complications of prematurity such as intracranial hemorrhage, necrotizing enterocolitis, sepsis, patent ductus arteriosus, retinopathy of prematurity, pulmonary hemorrhage, pneumonia, pneumothorax and BPD that were related to RDS were assessed out of which pulmonary hemorrhage, pneumonia, pneumothorax and BPD were found to be the most common cause of neonatal morbidity. (Agrons et al., 2005).

The use of antental steroid is associated with reduced severity of RDS and morbidity of the neonate. This factor is discussed later in this section.
NCPAP was used in neonates who had mild or moderate RDS. As per the European Consensus Guidelines for 2013, it was recommended that non - invasive respiratory support should be used at birth for all infants who are at risk for RDS. .(Sweet et al.,2013) (Mahmoud, Roehr and Schmalisch, 2011). A systematic review from Cochrane collaboration showed that use of CPAP in preterm infants with RDS significantly reduced treatment failure. In addition, a reduction in the need for additional mechanical ventilation was observed. (Ho, Henderson – Smart and Davis,2002). CPAP use was found to reduce the mortality among preterm with RDS. Neonates at higher risk of RDS/ severe RDS were given ventilator therapy which was in consistence with the study conducted by Morley et al. which revealed revealed that Non – invasive ventilation could not always provide effective oxygenation and stable the lung mechanics. Therefore mechanical ventilation remained an essential technique to care for preterm infants with RDS for whom non – invasive ventilation failed. (Morley et al., 2008). Mortality of RDS was found to be 9.50%.

When the general characteristics of the patient were compared before intervention a significant difference of p=0.017 was found with respect to gestational age which signified the use of surfactants was more in less than equal to 32 weeks group which was in accordance with a study conducted by Condo et al. the frequency of RDS decreased with increasing gestational age therefore, reducing the need for surfactant (Condo et al., 2016) and

with another study conducted by Enezi et al. majority of subjects were premature and underwent surfactant replacement therapy (A. Enezi et al., 2018).

A significant difference of p=0.012 was found with respect to birth weight which signified use of surfactants was more in <1,500 g group which was in consistence with a study conducted by Fehlmann et al. which revealed that use of surfactant and supportive therapy was more in preterm infants of very low birth weight. (Fehlmann et al., 2010). As per another study conducted by Enezi et al. one of the reasons for neonates undergoing surfactant therapy was low birth weight besides other factors like prematurity, transient tachypnea and respiratory failure. (A. Enezi et al., 2018).

A significant p value of 0.026 was found for pulmonary hemorrhage between the groups with number of neonates being more in survanta group.

When the general characteristics of the patient were compared after intervention in ≤32 weeks group a significant difference of p=0.010 was found with respect to NCPAP which signified that Curosurf group required least support it was in consistence with a study conducted by Ramanathan et al., in which effectiveness of Curosurf and Survanta was compared and it was found that a significantly lower oxygen demand was seen in curosurf group. (Ramanathan et al., 2004).

According to another study conducted by Bita Nafajian et al., efficacy and safety of Survanta and Curosurf were compared it was found that prescription of Curosurf was associated with lower CPAP or endotracheal tube requirement. (Nafajian et al., 2016).

As per a review article by Corff et al. the institutes were keen on extubating neonates post surfactant. A surfactant which is rapid acting and easy to administer can reduce the time to extubation to CPAP. (Corff et al., 2006).

General characteristsics of the neonates could not be compared in the >32 weeks group as only survanta was used.

When a two-by-two comparison of surfactants was done no significant difference was found between Survanta and Curosurf.

Between a two-by-two comparison of surfactants there was significant difference between Survanta and Neosurf group with a p value of 0.005 for NCPAP support. This signifies that

Neonates in the Neosurf group required less NCPAP support. No significance was found between other variables.

Between a two-by-two comparison of surfactants there was significant difference between Survanta and Neosurf group with a p value of 0.005 for NCPAP support. This signifies that Neonates in the Neosurf group required less NCPAP support. No significance was found between other variables.

But, when Neosurf and Curosurf were compared statistically significant difference was found between Curosurf and Neosurf group with a p value of 0.005 for NCPAP support. This signifies that neonates in the Curosurf group required less NCPAP support. No significance was found between other variables. Ad discussed earlier Curosurf required less oxygenation support.

Significant differences were found between pre and post values of Pco2. There was a statistically significant difference in pre and post values of pCO2 which is seen in the Survanta group(p=0.003) and Curosurf group(p=0.002). According to study conducted by Proquitte et al. the PCO2 values had significantly decreased after Curosurf administration. (Proquitte et al., 2007). According to a study conducted by Enezi et al. there was significant difference in pre-surfactant and post-surfactant values of Pco2 at p=0.001 (A. Enezi et al.,2018).

There was a statistically significant difference in pre and post values of BE in the Survanta group with a p value of 0.007**.** According to a study conducted by Enezi et al. there was statistical significance in pre and post base excess. (A. Enezi et al.,2018).

Severity of RDS among neonates with respect to comorbidities of the mother during the gestation period were grouped accordingly. As per a similar study conducted by Obladen, it was concluded that a retardation of pulmonary maturity was found to be seen in infants with maternal diabetes and maternal hypothyroidism. (Obladen, 1978). As discussed earlier hypertension and diabetes was found to show a major role in increasing the severity of RDS.

Among the neonates who had mild rds, following were the drugs taken by the mothers during the gestation periods; tt prophylaxis (37.82), fe/ca/folic acid prophylaxis (38.69%), labetalol (3.26%) and aspirin (3.26%). Among the neonates who had moderate rds, following were the

drugs taken by the mothers during the gestation periods; tt prophylaxis (38.9), fe/ca/folic acid prophylaxis (38.9), labetalol (3.05), aspirin (3.38) and levothyroxine (2.71) among the neonates who had severe rds, following were the drugs taken by the mothers during the gestation periods; tt prophylaxis (36.29%), fe/ca/folic acid prophylaxis (37.01%), neuroprophylaxis (2.84%), labetalol (2.84%), alphadopa (2.84%), aspirin (3.55%) and levothyroxine (3.20%).

A p value of 0.000 was found for APGAR 1 minute which indicates that there is a significant difference between the mild, moderate and severe groups. In mild RDS, the APGAR score was found to be higher (7.88±1.652) than moderate RDS (7.38±1.863) and moderate RDS had a higher score when compared with severe RDS (7.38±1.863). A p value of 0.000 was found for APGAR 5 minute which indicates that there is a significant difference between the mild, moderate and severe groups. In mild RDS, the APGAR score was found to be higher (8.77±0.648) than moderate RDS (8.73±0.620) and moderate RDS had a higher score when compared with severe RDS (7.5±1.768). In consistence with a study conducted by Chambliss and Bay, a 5 minute APGAR score of 7 or less was found to be an independent risk factor for RDS and therefore were very likely to develop RDS. (Chambliss and Bay, 2005).

Among neonates with gestational age ≤32 weeks, it was found that 88 (28.57%) neonates had mild RDS, 91 (10.06%) neonates had moderate RDS, and 129 (41.88%) neonates had severe RDS. Among neonates with gestational age >32 weeks, it was observed that 149 (63.13%) neonates had mild RDS, 63 (26.69%) neonates had moderate RDS and 24 (10.16%) neonates had severe RDS.

Among neonates of male gender, it was seen that 138 (42.33%) neonates had mild RDS, 92 (28.22%) neonates had moderate RDS and 96 (29.44%) neonates had severe RDS. Among neonates of female gender, 102 (44.34%) neonates had mild RDS, 64 (27.82%) neonates had moderate RDS and 64 (27.82%) neonates were found have severe RDS.

Comorbidities among neonates diagnosed with mild rds were found to be septic shock 1.03%, necrotizing enterocolitis 3.09%, pneumonia 4.12%, meningitis 4.12%, anemia of prematurity 7.21%, apnea of prematurity 8.24%, neonatal hyperbilirubinemia 46.39% and sepsis 25.77%.

Comorbidities among neonates diagnosed with moderate rds were found to be perinatal asphyxia 2.56%, septic shock 2.56%, necrotizing enterocolitis 2.56%, acidosis 1.28%, pneumonia 1.28%, meningitis 3.84%, anemia of prematurity 10.25%, apnea of prematurity 7.69%, neonatal hyperbilirubinemia 30.76% and sepsis 37.17%.

Comorbidities among neonates diagnosed with severe rds were found to be perinatal asphyxia 9.73%, septic shock 6.19%, meconium aspiration syndrome 0.88%, necrotizing enterocolitis 3.53%, acidosis 4.42% , pneumonia 5.30% , meningitis 3.53% , anemia of prematurity 13.27%, apnea of prematurity 1.76%, neonatal hyperbilirubinemia 15.92% and sepsis 35.39%.

It was revealed that when mothers were given with antenatal steroids, more number of neonates had mild (46.25%) RDS and moderate (23.33%) RDS in comparison with severe RDS. Hence from our study we can conclude that use of antenatal steroids can help reduce the severity of RDS in neonates. According to a study conducted by Heljic et al. it was concluded that antenatal corticosteroid administration significantly reduced the incidence and severity of RDS in premature neonates. It is recommended to initiate antenatal corticosteroid therapy among women between 24 and 34 weeks of gestation as early as preterm delivery appears to be likely. (Heljic et al.,2009). According to studies conducted by Crowley P., Wright et al. and Chien. it was concluded that antenatal steroids significantly reduced the mortality among neonates with respiratory distress syndrome. Among infants born at or earlier than 27 weeks gestation, the incidence of Respiratory distress syndrome was not found to be reduced after exposure to antenatal steroids although the severity seemed to be lower. (Crowley, 2006) (Chien, 2002) (Wright et al., 1995).

With respect to understanding the relationship between use of antenatal steroids and occurrence of death among neonates diagnosed with RDS; it was observed that 93.70% neonates had improved after the mother had received antenatal steroids while only 81.31% of neonates improved when no steroid was given. Mortality rate was found to be 6.29% in neonates who received antenatal steroids whereas it was 18.68% in neonates who did not receive antenatal steroids; this reveals that use of antenatal steroids reduced the mortality among neonates diagnosed with RDS. According to a study conducted by Shahzad et al. Initiation of antenatal steroid treatment has evolved as the most effective treatment for reducing early neonatal morbidity and mortality among women who are at risk of preterm delivery. (Shahzad F., Umar N., 2016).

LIMITATIONS

The general limitations for any retrospective study applies to our study as well.

- The paper on which the ABG values were printed fades over time and hence we could not collect ABG values for all patients.

- The number of patients who received Neosurf were very less when compared to Survanta and Curosurf.

CONCLUSION

This is the first retrospective study in South India conducted to compare the efficacy of three naturally occurring surfactants Survanta,Curosurf and Neosurf.
Demographics of 610 neonates with RDS showed that incidence of RDS is greater in males, the risk of RDS decreases with increasing gestational age and birth weight. The incidence of RDS increases with caesarean delivery and PROM, preeclampsia, IDM.

Among 610 neonates diagnosed with RDS, 191 received surfactant therapy. These neonates were then grouped based on the gestational age groups less than equal to 32 weeks and more than 32 weeks, two-by-two comparison of surfactants and ABG values pre and post surfactant it was concluded that neonates in less than or equal to 32 weeks of gestational age required surfactant therapy more than neonates in more than 32 weeks group, in less neonates in Curosurf group required lesser NCPAP support as compared to Survanta and Neosurf and there was a significant reduction in pCo2 values after surfactant administration, Survanta and Curosurf both showed significance.

Risk factors associated with RDS in neonates were assessed with respect to severity of RDS. It was found out that neonates whose mothers were having hypertension, type 2 diabetes mellitus, gestational diabetes and hypothyroidism during gestation were at higher risk of RDS. Mothers medications also could have affected the neonates risk of developing RDS. Factors such as gestational age of the neonate and 1 minute APGAR and 5 minute APGAR were found to be significant factors contributing in increasing the risk of RDS. Neonates comorbidities were studied and their relation with RDS severity was assessed.

Use of antental steroids significantly reduced the number of deaths and also reduced the severity of RDS.

REFERENCES

1. Agrons, G., Courtney, S., Stocker, J. and Markowitz, R. (2005). Lung Disease in Premature Neonates: Radiologic-Pathologic Correlation. *RadioGraphics*, 25(4), pp.1047-1073.

2. Al Hazzani, F., Al Hussein, K., Al Alaiyan, S., Al Saedi, S., Al Faleh, K., Al Harbi, F., Al-Salam, Z., Al Abdi, S., Al Harbi, A., Al Omran, A. and Azzouz, M. (2017). Mechanical ventilation in newborn infants: Clinical practice guidelines of the Saudi Neonatology Society. *Journal of Clinical Neonatology*, 6(2), p.57.

3. Anadkat, J., Kuzniewicz, M., Chaudhari, B., Cole, F. and Hamvas, A. (2012). Increased risk for respiratory distress among white, male, late preterm and term infants. *Journal of Perinatology*, 32(10), pp.780-785.

4. Ardell, S., Pfister, R. and Soll, R. (2015). Animal derived surfactant extract versus protein free synthetic surfactant for the prevention and treatment of respiratory distress syndrome. *Cochrane Database of Systematic Reviews*.

5. Chambliss, Linda R., Bay, R Curtis (2005); The Predictive Value of a 5-Minute Apgar for Developing Respiratory Distress Syndrome; Obstetrics & Gynecology: Volume 105 - Issue 4 - p 1S.

6. Chen, C., Wang, K., Chang, T., Chen, C. and Loo, J. (2005). Effects of Antenatal Betamethasone and Dexamethasone in Preterm Neonates. *Taiwanese Journal of Obstetrics and Gynecology*, 44(3), pp.247-251

7. Chien, L. (2002). Variations in antenatal corticosteroid therapy: a persistent problem despite 30 years of evidence. *Obstetrics & Gynecology*, 99(3), pp.401-408.

8. Condò, V., Cipriani, S., Colnaghi, M., Bellù, R., Zanini, R., Bulfoni, C., Parazzini, F. and Mosca, F. (2017). Neonatal respiratory distress syndrome: are risk factors the same in preterm and term infants?. *The Journal of Maternal-Fetal & Neonatal Medicine*, 30(11), pp.1267-1272.

9. Corff, K., Greubel, S., McCann, D., Williams, R. and Varner, D. (2006). Practical Considerations in the Selection and Use of Pulmonary Surfactant Therapy for Neonatal Respiratory Distress Syndrome in the Intensive Care Setting. *The Journal of Pediatric Pharmacology and Therapeutics*, 11(3), pp.161-168.

10. Crowley, P. (2006). Prophylactic corticosteroids for preterm birth. *Cochrane Database of Systematic Reviews*.

11. De Paoli, A., Davis, P., Faber, B. and Morley, C. (2008). Devices and pressure sources for administration of nasal continuous positive airway pressure (NCPAP) in preterm neonates. *Cochrane Database of Systematic Reviews*.

12. Dudell, G. and Jain, L. (2006). Hypoxic Respiratory Failure in the Late Preterm Infant. *Clinics in Perinatology*, 33(4), pp.803-830.

13. Enezi, F., Mohan, S., Alghamdi, K., D. Alenzi, A., Ahmed Alrashidi, K., A. Almajed, A., Eid Alqithami, F., Philip, W. and Qureshi, S. (2018). Incidence and Outcome of

Surfactant Therapy in Premature Neonates in ICU of KAMC. *International Journal of Current Microbiology and Applied Sciences*, 7(04), pp.1548-1558.

14. Fehlmann, E., Tapia, J., Fernández, R., Bancalari, A., Fabres, J., D'Apremont, I., García-Zattera, M. and Grandi, C. (2010). Impact of respiratory distress syndrome in very low birth weight infants: a multicenter South-American study. 108 (5).

15. Fidanovski, D., Milev, V., Sajkovski, A., Hristovski, A., Sofijanova, A., Kojic, L. and Kimovska, M. (2005). Mortality risk factors in premature infants with respiratory distress syndrome treated by mechanical ventilation. *Srpski arhiv za celokupno lekarstvo*, 133(1-2), pp.29-35.

16. Ghartey, K., Coletta, J., Lizarraga, L., Murphy, E., Ananth, C. and Gyamfi-Bannerman, C. (2012). Neonatal respiratory morbidity in the early term delivery. *American Journal of Obstetrics and Gynecology*, 207(4), pp.292.e1-292.e4.

17. Goldenberg, R., Culhane, J., Iams, J. and Romero, R. (2008). Epidemiology and causes of preterm birth. *The Lancet*, 371(9606), pp.75-84.

18. Hansen, A., Wisborg, K., Uldbjerg, N. and Henriksen, T. (2007). Risk of respiratory morbidity in term infants delivered by elective caesarean section: cohort study. *BMJ*, 336(7635), pp.85-87.

19. Heljić, S., Maksić, H., Kalkan, I. and Krđalić, B. (2009). The Effects of Antenatal Corticosteroids and Surfactant Replacement on Neonatal Respiratory Distress Syndrome. *Bosnian Journal of Basic Medical Sciences*, 9(3), pp.225-228.

20. Ho, J., Henderson-Smart, D. and Davis, P. (2002). Early versus delayed initiation of continuous distending pressure for respiratory distress syndrome in preterm infants. *Cochrane Database of Systematic Reviews*.

21. Kumar, A. and Vishnu Bhat, B. (1996). Epidemiology of respiratory distress of newborns. *The Indian Journal of Pediatrics*, 63(1), pp.93-98.

22. Mahmoud, R., Roehr, C. and Schmalisch, G. (2011). Current methods of non-invasive ventilatory support for neonates. *Paediatric Respiratory Reviews*, 12(3), pp.196-205.

23. Melamed, N., Klinger, G., Tenenbaum-Gavish, K., Herscovici, T., Linder, N., Hod, M. and Yogev, Y. (2009). Short-term Neonatal Outcome in Low-Risk, Spontaneous, Singleton, Late Preterm Deliveries. *Obstetrics & Gynecology*, 114(2, Part 1), pp.253-260.

24. Melamed, N., Klinger, G., Tenenbaum-Gavish, K., Herscovici, T., Linder, N., Hod, M. and Yogev, Y. (2009). Short-term Neonatal Outcome in Low-Risk, Spontaneous, Singleton, Late Preterm Deliveries. *Obstetrics & Gynecology*, 114(2, Part 1), pp.253-260.

25. Morley, C., Davis, P., Doyle, L., Brion, L., Hascoet, J. and Carlin, J. (2008). Nasal CPAP or Intubation at Birth for Very Preterm Infants. *Obstetric Anesthesia Digest*, 28(4), pp.226-227.

26. Mwansa-Kambafwile, J., Cousens, S., Hansen, T. and Lawn, J. (2010). Antenatal steroids in preterm labour for the prevention of neonatal deaths due to complications of preterm birth. *International Journal of Epidemiology*, 39(Supplement 1), pp.i122-i133.

27. Najafian, B., Karimi-Sari, H., Khosravi, M., Nikjoo, N., Amin, S. and Shohrati, M. (2016). Comparison of efficacy and safety of two available natural surfactants in Iran, Curosurf and Survanta in treatment of neonatal respiratory distress syndrome: A randomized clinical trial. *Contemporary Clinical Trials Communications*, 3, pp.55-59.

28. Namavar Jahromi, B., Ardekany, M. and Poorarian, S. (2000). Relationship between duration of preterm premature rupture of membranes and pulmonary maturation. *International Journal of Gynecology & Obstetrics*, 68(2), pp.119-122.

29. NNPD Network. Neonatal Neonatal Perinatal Database, Report 2002–2003. Deorari A, ed. New Delhi: Indian Council of Medical Research; 2005

30. Obladen, M. (1978). Factors influencing surfactant composition in the newborn infant. European Journal of Pediatrics, 128(3), pp.129-143.

31. Piper, J., Xenakis, E. and Langer, O. (1998). Delayed appearance of pulmonary maturation markers is associated with poor glucose control in diabetic pregnancies. *The Journal of Maternal-Fetal Medicine*, 7(3), pp.148-153.

32. Proquitté, H., Dushe, T., Hammer, H., Rüdiger, M., Schmalisch, G. and Wauer, R. (2007). Observational study to compare the clinical efficacy of the natural surfactants Alveofact and Curosurf in the treatment of respiratory distress syndrome in premature infants. *Respiratory Medicine*, 101(1), pp.169-176.

33. Pugni, L., Colnaghi, M., Lattanzio, M., Cecchetti, V., Giuffre, B., Compagnoni, G., Mosca, F. and Marini, A. (1999). Maternal Preeclampsia as a Risk Factor for Respiratory Distress Syndrome in "Small for Gestational Age" Infants. *Pediatric Research*, 45(4, Part 2 of 2), pp.316A-316A.

34. Ramachandrappa, A. and Jain, L. (2008). Elective Cesarean Section: Its Impact on Neonatal Respiratory Outcome. *Clinics in Perinatology*, 35(2), pp.373-393.

35. Ramanathan, R., Rasmussen, M., Gerstmann, D., Finer, N. and Sekar, K. (2004). A Randomized, Multicenter Masked Comparison Trial of Poractant Alfa (Curosurf) versus Beractant (Survanta) in the Treatment of Respiratory Distress Syndrome in Preterm Infants. *American Journal of Perinatology*, 21(3), pp.109-119.

36. Respiratory Distress Syndrome;National Heart, Lung and Blood Institute; National Institute of Health.

37. Roberts, D., Brown, J., Medley, N. and Dalziel, S. (2017). Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database of Systematic Reviews*.

38. Rubaltelli, F., Bonafè, L., Tangucci, M., Spagnolo, A. and Dani, C. (1998). Epidemiology of Neonatal Acute Respiratory Disorders. *Neonatology*, 74(1), pp.7-15.

39. Shahzad F., Umar N.(2016); Impact of antenatal corticosteroids on frequency and mortality due to respiratory distress syndrome in preterm neonates; J Ayub Med Coll Abbottabad ;28(4):698–701.

40. Singh, N., Halliday, H., Stevens, T., Suresh, G., Soll, R. and Rojas-Reyes, M. (2015). Comparison of animal-derived surfactants for the prevention and treatment of respiratory distress syndrome in preterm infants. *Cochrane Database of Systematic Reviews*.

41. Subramaniam, P., Ho, J. and Davis, P. (2016). Prophylactic nasal continuous positive airway pressure for preventing morbidity and mortality in very preterm infants. *Cochrane Database of Systematic Reviews*.

42. Sun, H., Xu, F., Xiong, H., Kang, W., Bai, Q., Zhang, Y., Zhou, C., Zhuang, F., Wang, X. and Zhu, C. (2013). Characteristics of Respiratory Distress Syndrome in Infants of Different Gestational Ages. *Lung*, 191(4), pp.425-433.

43. Sweet, D., Carnielli, V., Greisen, G., Hallman, M., Ozek, E., Plavka, R., Saugstad, O., Simeoni, U., Speer, C., Vento, M. and Halliday, H. (2013). European Consensus Guidelines on the Management of Neonatal Respiratory Distress Syndrome in Preterm Infants - 2013 Update. *Neonatology*, 103(4), pp.353-368.

44. Tridente, A., De Martino, L. and De Luca, D. (2019). Porcine vs bovine surfactant therapy for preterm neonates with RDS: systematic review with biological plausibility and pragmatic meta-analysis of respiratory outcomes. *Respiratory Research*, 20(1).

45. Whitsett, J. and Stahlman, M. (2010). Circulatory Factors in Relation to Idiopathic Respiratory Distress (Hyaline Membrane Disease) in the Newborn. *The Journal of Pediatrics*, 156(5), p.723.

46. Wright, L., Horbar, J., Gunkel, H., Verter, J., Younes, N., Andrews, E. and Long, W. (1995). Evidence from multicenter neworks on the current use and effectiveness of antenatal corticosteroids in low birth weight infants. *American Journal of Obstetrics and Gynecology*, 173(1), pp.263-269.

47. Yee, W., Amin, H. and Wood, S. (2008). Elective Cesarean Delivery, Neonatal Intensive Care Unit Admission, and Neonatal Respiratory Distress. *Obstetrics & Gynecology*, 111(4), pp.823-828.

APPENDIX

APPENDIX-1

KASTURBA HOSPITAL
MANIPAL
(An Associate Hospital of MAHE, Manipal)

Kasturba Medical College and Kasturba Hospital
Institutional Ethics Committee
(Registration No. ECR/146/Inst/KA/2013/RR-16)

Communication of the decision of the Institutional Ethics Committee

Saturday 09th March 2019 **IEC : 399/2018**

Project title	:	Use of Surfactants in the treatment of Neonatal Respiratory Distress Syndrome.
Principal Investigator	:	Miss. Pareeta Kotecha
Guide/ Co Guide/ Co Investigators	:	Rupal Francisca Aroza, Rajesh V, Dr. Leslie Edward Lewis, M. Surulivel Rajan
Name & Address of Institution	:	Department of Pharmacy Practice, Manipal College of Pharmaceutical Sciences, MAHE, Manipal, Department of Paediatrics, KMC, Manipal, Department of Pharmacy Practice, Manipal College of Pharmaceutical Sciences, MAHE, Manipal.
Status of review	:	New
Date of review	:	10.07.2018
Amendment	:	Modified on 09.03.2019
Decision of the IEC	:	Approved for the study period from 10.07.2018 to 09.07.2019 as mentioned in protocol with the change in title and objectives.

- The PI and all members of the project shall ensure compliance to current regulatory provisions (as per Schedule Y of Drugs and Cosmetics Act and ICH-GCP), Ethical Guidelines for Biomedical Research on Human Participants by ICMR, and the SOP of IEC including timely submission of Interim Annual Report and Final Closure Report
- Participant Information Sheet and a copy of signed Informed Consent shall be given to every research participant
- Inform IEC in case of any proposed amendments (change in protocol / procedure, site / Investigator etc)
- Inform IEC immediately in case of any Adverse Events and Serious Adverse Events.
- Members of IEC have the right to monitor any project with prior intimation.

Dr. Rajeshkrishna Bhandary P
MEMBER SECRETARY - IEC

ETHICS COMMITTEE APPROVED KASTURBA HOSPITAL MANIPAL

IEC Secretariat, Room No. 22, Ground Floor, Faculty Room Complex, Kasturba Medical College Premises,
Kasturba Medical College, Manipal - 576104, Karnataka, India. Phone : +91 - 0820 - 2933522,Fax : +91 - 0820 - 2571927. Email : iec.kmc@manipal.edu

MR-798

(Yoga and Ayurveda services are excluded from the scope of NABH accreditation)

APPENDIX-2

PATIENT DATA COLLECTION FORM

Hospital ID No:		Gestational Age:	Sex:
Weight:		APGAR SCORE:	
Diagnosis			
Medication History			
Comorbidities	Transient tachypnea/ Pneumonia/ Sepsis/ Meningitis/ aspiration		
	Others, if any:		
Multiple Pregnancy		Yes	No
Mother's History			
Mother's Medication History			
Mode of delivery		Vaginal	Caesarean
Preterm rupture of membrane		Yes	No
Preeclampsia		Yes	No
IDM		Yes	No
Duration of Hospital stay			
Ventilation time (days)			
No. Surfactant Injection(s)			
Betamethasone		Yes	No
Dexamethasone		Yes	No

Different Variables among Neonates Receiving Surfactant after Intervention

Surfactant used:

Characteristics:		
Pneumothorax	Yes	No
Patent Ductus Arteriosus	Yes	No
Retinopathy	Yes	No
Bronchopulmonary dysplasia	Yes	No
Intracranial haemorrhage	Yes	No
Pulmonary haemorrhage	Yes	No
Ventilator therapy	Yes	No
NCPAP support	Yes	No

Variable	Pre-Surfactant	Post-Surfactant
pH		
pCO2		
pO2		

Drug Chart:

Drug Prescribed	Dose Prescribed	Dose Adjusted	Frequency	Duration

Clinical Outcome

Positive Outcome	
Negative Outcome	

APPENDIX-3

ORIGINALITY REPORT

13%	9%	9%	3%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	link.springer.com Internet Source	2%
2	www.ncbi.nlm.nih.gov Internet Source	1%
3	www.ijcmr.com Internet Source	1%
4	J.A. Whitsett. "Respiratory Distress Syndrome-Hyaline Membrane Disease☆", Elsevier BV, 2014 Publication	1%
5	Chen-Yu Chen, Kuo-Gon Wang, Tung-Yao	1%