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Outcomes Of Surfactant Therapy In Newborns With Respiratory Distress Syndrome In Relation To Age Of Presentation To NICU Of MGM Hospital.

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ABSTRACT
BACKGROUND:RDS is usually defined by the presence of acute respiratory distress with disturbed gas exchange in a preterm infant with a typical clinical course or x-ray.The main risk factor for RDS,by far,is prematurity.The central feature of RDS is surfactant deficiency due to lung immaturity,commonly due to prematurity.Surfactant replacement therapy reduces mortality and several aspects of morbidity in babies with RDS.
METHODS:Newborns with RDS were intubated with endotracheal tube and surfactant was administered.The first dose of surfactant was given as early as possible to the preterm infants requiring MV for RDS then extubated and connected to nasal CPAP.The mortality,morbidities were compared.
RESULTS: Among the 150 preterms who were recruited in this study, outcomes of surfactant therapy is discussed in correlation with the time of presenation,hour of installation of surfactant,birth weight,gestational age,size for gestational age, severity of RDS,surfactant doses,length of hospital stay,type of assisted ventilation,duration of assisted ventilation,duration of supplemental oxygen,complications with surfactant therapy.We found that surfactant replacement therapy has a beneficial effect.
CONCLUSION:Out of 150 preterms with RDS who are more than 31 weeks of gestation,more than 1500 grams,appropriate for gestational age,Singleton neonates,mild and moderate respiratory distress,and who received single dose of surfactant with RDS, had better outcome and discharged.45.3% of the preterm new born who were given surfactant had fatal outcome.Only 54.7% of preterm newborns who were given surfactant have discharged.
KEY WORDS:Respiratory distress syndrome(RDS),surfactant, preterm.

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INTRODUCTION

Neonatal and perinatal mortality rates are the major indicators for the health status of the nation. In developed countries, the neonatal and perinatal mortality rates are 3–5 and 8–9 per 1000 live births respectively. In India current neonatal mortality rate (NMR) is 22 per 1000 live births (2019) of which urban NMR is 14 and rural NMR is 27.In which prematurity account for 35% as per Health and Family Welfare Statistics in India 2019-20 [1]. In developed countries, improved diagnosis and treatment due to technical advancements and increased pediatric and neonatal specializations have led to an impressive fall in neonatal mortality. In India, in spite of advancement in the field of neonatology, there is not much decline in the incidence of neonatal mortality and morbidity.

Respiratory distress is one of the commonest problems of newborns occurring throughout the world. It is usually defined by the presence of acute respiratory distress with disturbed gas exchange in a preterm infant with a typical clinical course (Tachypnea, Grunting, Increased work of breathing, Nasal flaring). The main risk factor for RDS, by far, is prematurity. Other factors that increase the risk of RDS include perinatal asphyxia, maternal diabetes, lack of labor, absence of antenatal steroid administration to the mother, male gender. The central feature of RDS is surfactant deficiency due to lung immaturity, commonly a result of premature birth or delayed lung maturation associated with maternal diabetes or male gender. The incidence of respiratory distress varies in relation to various predisposing and underline factors like gender, gestational age, body weight, poor infrastructure, lack of skilled health resources, poor monitoring system etc. Surfactant deficiency at birth makes it difficult for the newborns to inflate its lungs. Immature lungs of preterm are deficient in surfactant which leads to RDS. The lungs of preterm babies with RDS are both anatomically and biochemically immature; they neither synthesize nor secrete surfactant well. Surfactant normally lines the alveolar surfaces in the lung, thereby reducing surface tension and preventing atelectasis.

Surfactant replacement therapy (SRT) is now accepted as the standard treatment protocol for preterm babies with HMD [2] .Surfactant therapy given early, reduces mortality and several aspects of morbidity in babies with RDS. Morbidities include deficits in oxygenation, the incidence of pulmonary air leaks (pneumothorax and pulmonary interstitial emphysema) and the duration of ventilatory support. Administration of natural surfactant reduces acute respiratory disease, air leaks, bronchopulmonary dysplasia, and mortality in preterm infants[3].Babies treated with surfactants have shorter hospital stays and lower costs of intensive care treatment. The current use of exogenous surfactant in neonates with RDS has greatly reduced the morbidity and mortality rates of neonates suffering from this disease. Respiratory failure secondary to surfactant deficiency is a major cause of morbidity and mortality in preterm infants. Surfactant therapy substantially reduces mortality and respiratory morbidity for this population.

The evidence-based practices for early recognition and appropriate therapy of neonatal respiratory disease may have impressive results in modern medicine. The present study was undertaken with the aim to know the most common etiological factors responsible for neonatal

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respiratory distress and the effect of modern advancements like surfactant, bubble CPAP and mechanical ventilation on the outcome of newborns with severe distress.

METHODS

Aim of the study

To determine the outcome of surfactant therapy with age of presentation in the prognosis of Respiratory distress syndrome.

Objectives of the study

a) To assess the effects of early versus late administration of surfactant.
b) To evaluate the various other parameters that can predict the outcome of surfactant therapy.

Source of data:

All respiratory distress syndrome cases admitted in NICU of Mahatma Gandhi memorial hospital (MGMH) attached to Kakatiya medical college with respiratory distress syndrome.

Sample size:

All babies admitted in NICU with respiratory distress syndrome needing surfactant during time period November 2018 to November 2020.

Inclusion criteria

All preterm neonates who are admitted in NICU with features of respiratory distress syndrome (1) Tachypnea; (2) grunting; (3) increased demand of oxygen; (4) Radiographic findings are included.

Exclusion criteria

Term neonates.
Nasopharyngeal pathology (cleft lip and cleft palate, choanal atresia).
Major congenital anomalies especially thoracic and cardiac defects.
Pneumonia and incompletely treated pneumothorax.
Babies diagnosed with meconium aspiration syndrome.

Type of study:

Prospective Observational Study.

Study period:

From November 2018 to November 2020.

Statistical analysis:

Data was entered into Microsoft Excel (Windows 7; Version 2007) and analyses were done using the Statistical Package for Social Sciences (SPSS) for Windows software (version 22.0; SPSS Inc, Chicago). Descriptive statistics such as mean and standard deviation (SD) for continuous Variables, frequencies and percentages were calculated for categorical Variables were determined. Association between Variables was analyzed by using Chi-Square test for categorical Variables. Bar charts and Pie charts were used for visual representation of the analyzed data. Level of significance was set at 0.05.

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RESULTS AND OBSERVATIONS.

In the Table 1,Correlation taken between categorical variables which influenced the outcome of surfactant installation and Fisher exact Test, P Value calculated.

It became evident that higher the gestational age better the outcome(discharge rate) with surfactant therapy showing significant correlation (<0.001).Small for gestational age babies who got surfactant therapy had adverse outcome(100% death) whereas the appropriate for gestational age group had better outcome showing significant correlation (0.013). When compared to twins, single gestation babies who were given surfactant had good outcome with good discharge rate(80%) and statistically significant (0.050).There is no strong association between surfactant doses and outcome in this study. Giving CPAP ventilation after surfactant therapy had a better outcome (79.6%) than mechanical ventilation and its statistically significant(<0.001).

In the Table 2,Correlation taken between categorical variables which influenced the outcome of surfactant installation and Unpaired t Test, P Value calculated.

We observed that higher the birthweight better the outcome showing good association(<0.001) between birthweight and outcome with surfactant therapy.When SAS score is taken into consideration, less severe the SAS more discharge rate is observed showing strong association between outcome and severity of respiratory distress.Taking length of hospital stay into consideration, babies who stayed longer than 1 week had good outcome showing strong correlation between length of hospital stay and surfactant therapy (<0.001).

When time of presentation and installation of surfactant taken into consideration and correlated with the outcome, results are tabulated in table 3.They presented in the range of 1 to 192 hours of life and are given surfactant based on the hour of presentation. There is no significant correlation between hour of installation of surfactant with respect to hour of presentation in our study

In table 4 overall outcome Of the 150 study subjects who were given surfactant is tabulated, among them 68(45.3%) were died and 82(54.7%) have been discharged.

In the table 5, Out of the 150 babies who were enrolled in the study 2 babies (1.3%) had air leak as complication,22(14.7%) had apnea,1 baby (0.7%) had BPD/CLD,16(10.7%) had hypotension,1 baby (0.7%) had IVH,25 babies (16.7%) had pulmonary hemorrhage as complication, and the remaining 83(55.3%) had no complications.

DISCUSSION

Among the 150 preterm newborns who were recruited in this study, outcomes of surfactant therapy is discussed.

In the present study mean gestational age of the babies receiving surfactant therapy is 30.43 weeks which is close to the studies done by Manandhar SR et al [4] (30.1+/- 2.6 weeks) and Dr V. V. Vijayalakshmi, et. al [5] (30 +/- 1.57 weeks). Babies with more than 31 weeks of gestation with RDS who were given surfactant had better outcome with being similar to Manandhar SR et al [4] study. And babies who are born before 28 weeks of gestation had worse outcome and this outcome is similar in Hameed NN et al [6] study.

Neonatal mortality was significantly higher in SGA infants in the study of Atul Malhotra et al [7] study and nearly same results are seen in our study and correlation was statistically significant in both studies.

Correlation was also made between type of gestation and its outcome after instillation of surfactant. In study of Hameed NN et al [6] who were given surfactant Singleton 69.23% Twins 20.19% Triplets 9.62% Quadruplets 0.96% of preterm neonates were observed. In our study no triplet and quadruplets were observed but singleton 88% twins are 12% and there is significant correlation between number of births and their outcome.

Our study is almost similar to Phuljhele S et al [8] in terms of correlation of birth weight to its outcomes after surfactant instillation, mainly the neonates in the weight group of 1000-1499 grams and those with less than 1000 grams. Main limitation in the study of Manandhar SR et al [4] is that the sample size is only 30 preterm babies and the correlation is also not statistically significant.

Phuljhele S et al [8] showed that there is comparatively higher survival rate in patients receiving early surfactant therapy compared to late rescue therapy. In Hameed NN et al [6] there is higher survival rate in late surfactant therapy. But in our study there is no strong correlation between early rescue and late rescue therapy if surfactant is replaced.

Distribution of newborns based on degree of severity of respiratory distress in Vinayak Y. Kshirsagar et al [9] is as follows mild RDS as 23% moderate RDS 50% severe RDS 27%.In our study the distribution is as follows mild RDS as 7.3% moderate RDS 86.0% severe RDS 6.7% with mean SAS score of 4.97 leading to death, and newborns with mean 4.43 SAS score got discharged. This observation is statistically significant with p value 0.038.

In our study, surfactant replacement therapy was given to this 150 preterm new born based on their hour of presentation(hour of life) to the NICU. As our unit doesn't have an inborn admissions, most of the newborns are referred from nearby hospitals as our unit is tertiary care centre.For preterm newborns presenting within 6 hours of life mean time for surfactant replacement therapy is 1.61hours and among those presenting after 6 hours mean time for surfactant replacement therapy is 11.67 hours. There is no significant correlation between these two.

There was no correlation between doses of surfactant and outcome. Among them only 5(3.3%) preterm babies needed second dose. And remaining 145(96.7%) received one dose. This dosage relation is correlated with outcome and compared with other studies. None of the studies when compared found to be having no correlation with number of doses to the outcome of the babies.

In our study there was a greater relation between the hospital stay after surfactant administration and the outcome. This relation is compared between various studies. In The Study Done By Manandhar SR et al [4] 14.95+/-6.25 days was the mean hospital stay which is close to our study of

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10.85 mean days. This duration of stay in our study is statistically significant showing those who stayed for more than 7 days had good outcome and discharged well and those who expired are mostly in the group who stayed less than 7 days. We again studied length of NICU stay in relation to weight of the baby and 11 babies weighing less than 1500 grams who received surfactant stay for more than 3 weeks in KMC(kangaroo mother care) ward for weight gain. Babies who are mostly above 1500 grams discharge mostly by 2 weeks.

Of the 150 preterm newborns who were enrolled in the study 32.7% required CPAP and remaining 67.3% required mechanical ventilation, those who requiring CPAP has comparatively better outcome than those who requiring mechanical ventilation. Our study is similar to Henrik Verder et al [10] and Maryam nakshab et al [11] in which comparatively more percentage of newborns are discharged and this association is statistically significant with P Value <0.

In regarding to mechanical ventilation following surfactant administration the correlation is compared in various studies. in the study done by Peter A Dargaville et al [12] 55% neonates required mechanical ventilation Vinayak Y. Kshirsagar et al [9] it is 54.44%.but in our study 67.3% newborns needed mechanical ventilation which is close to the study of Peter A Dargaville et al [12].

Preterm newborns who received assisted ventilation following surfactant administration 66 newborns required oxygen and requiring at a mean of 4.05 days which is similar to the studies done by Maryam nakshab et al [11] and Dr V. V. Vijayalakshmi, et. al [5]

In our study there were many complications observed during the course of illness following surfactant replacement therapy for respiratory distress syndrome, similar complications are observed in many studies and most of them are air leak, bronchopulmonary dysplasia, Intraventricular haemorrhage, Pulmonary haemorrhage. In our study we observed many pulmonary haemorrhage babies during post surfactant and it was the main cause of death and second most cause for the death is apnea. But in many other studies most common complication observed is hypotension.

Main objective of surfactant replacement therapy to preterm neonates is to reduce mortality and morbidity pattern that is observed in respiratory distress syndrome. In the 150 preterm neonates we studied about the outcome following the surfactant replacement therapy and this observation is compared with many other international and Indian studies. The study revealed that there is 54.7 % survival rate if surfactant is replaced in preterm neonates with respiratory distress syndrome. As surfactant administration is a cost effective intervention, its role is invaluable in those NICUs where resources are limited. Early initiation of CPAP (to keep the alveoli open) with subsequent selective surfactant administration lowers mortality in preterm with RDS. Our study indicates that in INSURE technique, administration of surfactant together with ventilation with CPAP has an add on effect in preventing collapse of alveoli thereby effectively retarding

the further progression of RDS in preterm babies. Outcome in our study is similar to the study done by Hameed NN et al [6] where comparatively there is good outcome.

CONCLUSION

Out of 150 preterm newborns who required surfactant replacement therapy belonged to mean gestational age of 30.43 weeks. Neonates with more than 31 weeks of gestation with RDS who were given surfactant had better outcome and discharged.

Neonatal mortality was significantly higher in small for gestational age newborns who were given surfactant in the study. Better outcome is seen in neonates who are appropriate for gestational age. Singleton neonates who received surfactant replacement had better outcome than twin babies in the study.Preterm Neonates who were given surfactant therapy belonged to mean weight of 1486 grams. And those with less than 1000 grams had high chance of mortality and those with more than 1500 grams weight had higher chances of survival.Late rescue surfactant therapy had comparatively better outcome than early rescue therapy for RDS preterm newborns in our study. In regard to the hour of presentation to NICU surfactant was administered and with preterms presenting in less than 6 hours surfactant was administered at 1.61 mean hours and those who presented after 6 hours surfactant was administered at 11.67 mean hours.Preterms with RDS who received single dose of surfactant had discharged well and those with second dose of surfactant has equal outcomes, showing there is no advantage of using second dose in this study.38% of preterms newborns have died within 7 days of NICU stay after installation of surfactant and 53% preterms have survived when they had more than 7 days of NICU stay.Assisted ventilation following surfactant replacement therapy had better outcome when CPAP is used with 79.6% of them discharged. If mechanical ventilation is used after surfactant replacement therapy 57.4% of them have expired.Preterm neonates with severe respiratory distress syndromes based on SAS Score with mean SAS score of 4.97 had expired, and newborns with mean 4.43 SAS score got discharged.Many complications were encountered in the course of management with surfactant replacement therapy for RDS. Of them pulmonary haemorrhage, apnoea, hypotension are the common complications that are observed in the study.45.3% of the preterm newborns who were given surfactant had fatal outcome. Only 54.7% of preterm newborns who were given surfactant have discharged. This study supports and strengthens the favourable outcome of early and prophylactic surfactant therapy (over delayed rescue treatment strategy) that can be applicable even at resource limited settings.The maximum impact of survival was seen among the preterm babies of 30-36 weeks gestation and birth weight group of 1500 -2500 grams. This study has also shown that SRT followed by Bubble CPAP has significantly reduced the subsequent need for mechanical ventilation.This study recommends that Infants who are at a significant risk of RDS may need to be stabilized first and then given the surfactant and rapid weaning to CPAP and also improve infection control in NICU.In preterm neonates with RDS who are stabilized on CPAP, the SurE technique for surfactant delivery results in a reduced need for MV and also may decrease the rate of BPD.

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Table 1: Distribution of Study Subjects according Gestational age, Size and Type of gestation, surfactant doses, oxygen administration and assisted ventilation (N=150).

	Parameter	Outcome		P Value
		Death (%)	Discharged(%)	
GESTATIONAL AGE (as per Ballard's)	<28	18 (90.0)	2 (10.0)	<0.001*
	28-30	27 (71.1)	11 (28.9)	
	31-33	19 (28.4)	48 (71.6)	
	34-36	4 (16.0)	21 (84.0)	
SIZE FOR GESTATIONAL AGE	SGA	5 (100.0)	0	0.013*
	AGA	63 (43.4)	82 (56.6)	
TYPE OF GESTATION	Singleton	56 (42.4)	76 (57.6)	0.050*
	Twin	12 (66.7)	6 (33.3)	
SURFACTANT DOSES	1	65 (44.8)	80 (55.2)	0.503
	2	3 (60.0)	2 (40.0)	
OXYGEN ADMINISTRATION	No	2 (2.4)	82 (97.6)	<0.001*
	Yes	66 (100.0)	0	
ASSISTED VENTILATION	CPAP	10 (20.4)	39 (79.6)	<0.001*
	Mechanical Ventilation	58 (57.4)	43 (42.6)	
Fisher exact Test, P Value *Significant				

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Table 2 : Distribution of Study Subjects according to the birth weight, SAS score, Length of hospital stay(N=150).

Parameter	Outcome		P Value
	Death Mean (SD)	**Discharged Mean (SD)**	
Birth Weight (kg)	1.17 (0.30)	1.74 (0.41)	<0.001*
SAS Score at Admission	4.97 (1.81)	4.43 (1.37)	0.038*
Length of Hospital Stay (Days)	4.16 (5.21)	17.01 (9.69)	<0.001*
Unpaired t Test, P Value *Significant			

Table 3: Association between Time of Presentation and Hours of Installation of Surfactant (N=150.

Time Of Presentation (Hours)	Hours of Installation of Surfactant		Outcome	
	Early	**Late**	**Death n (%)**	**Discharged n (%)**
1	13 (54.2)	11 (45.8)	10 (41.7)	14 (58.3)
1-6	4 (4.9)	77 (95.1)	37 (45.7)	44 (54.3)
7-12		16 (100.0)	8 (50.0)	8 (50.0)
13-24		15 (100.0)	5 (33.3)	10 (66.7)
>24		14 (100.0)	8 (57.1)	6 (42.9)
Mean (SD)	1.61 (1.64)	11.67 (23.90)		
Chi-Square Test, P Value = 0.748, Not Significant				

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Table 4: Distribution of Study Subjects according to the Outcome (N=150).

Outcome	**No.**	**Percent**
Death	68	45.3
Discharged	82	54.7

Table 5: Distribution of Study Subjects according to the Complications (N=150).

Complications	**No.**	**Percent**
Air Leak	2	1.3
Apnea	22	14.7
BPD	1	0.7
Hypotension	16	10.7
IVH	1	0.7
Pulmonary Hemorrhage	25	16.7
Absent	83	55.3