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STUDY OF MORBIDITY AND MORTALITY PROFILE OF SURFACTANT THERAPY IN PRETERM VERY LOW BIRTH WEIGHT NEONATES IN NICU AT A TERTIARY CARE CENTRE OF WESTERN INDIA

Paediatric Medicine

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ABSTRACT

Introduction: Prematurity an important cause of Respiratory Distress Syndrome (RDS) and neonatal mortality. Complications of prematurity are becoming more common as more survivors are spending time in the NICU. Surfactant therapy is becoming increasingly common for such cases. Study aimed to describe the morbidity and mortality profile of surfactant therapy in preterm Very Low Birth Weight (VLBW) neonates. **Material and Methods:** This hospital based observational study included 110 Preterm VLBW neonates with RDS who were admitted and given Surfactant in NICU. Study included Preterm VLBW neonates of gestation age 28 to 34 weeks and birth weight 500- 1500gms. Preterm neonates with severe congenital malformations and chromosomal defects were excluded from the study. Respiratory distress was assessed by Silverman scoring. **Observations:** Majority (41.8%) Neonates had Birth weight of 1000 to 1249 gm. Only 8 (7.3%) mothers had taken Antenatal steroids. Majority of neonates (40.9%) had SAS score of 5 on admission. Only 13 (11.8%) neonates already received surfactant before admission and 24 (21.8%) were given repeat dose of surfactant. Septicemia (59%), Apnea (20%) and Shock (12.7%) were the major complications. In hospital mortality occurred in 22 (20%) neonates. Lower birth weight, High SAS score at admission, delayed cry after birth, and need for repeat dose were significantly associated with higher mortality. **Conclusion:** The use of surfactant therapy improved the survival outcome and decreased the associated morbidities with respiratory distress syndrome. Highest survival benefit was seen among the VLBW newborns with birth weight >1000 grams, Gestational age between 32- 34 weeks, Silverman Anderson score of >6 at the time of admission, and who were given early surfactant.

KEYWORDS

Preterm, Low Birth Weight, Surfactant, Silverman Anderson Score

INTRODUCTION:

Low birth weight (LBW), birth weight of 2500 g or less can be due to prematurity or intrauterine growth retardation or both. Very low birth weight (VLBW) (birth weight< 1500 gram) babies constitute approximately 4-7% of all live births and mortality amongst these neonates is very high. Survival of these babies is associated with their birth weight, gestation and illness severity [1]. Live born infant delivered before 37 weeks from the 1st day of last menstrual period are termed as "premature" [2]. Preterm birth is a major cause of morbidity and mortality of newborns and imposes a considerable burden on limited health care resources.

Prematurity is not only an important cause of mortality, but it also increases the risk of serious lifetime disabilities [3,4]. Primary complications include Infections, Respiratory Distress Syndrome (RDS), Bronchopulmonary Dysplasia, Necrotizing Enterocolitis, Intraventricular Hemorrhage, Patent Ductus Arteriosus (PDA) and Retinopathy of Prematurity [1]. However, despite all the advances in neonatal and perinatal care the morbidity among preterm babies still remains significantly high in developing countries. Some of these babies die during or after delivery, with surviving babies developing complications [1].

First 48 hours immediately following birth is the most crucial period for newborn survival [5].Complications of prematurity are becoming more common as more survivors are spending time in the NICU [3]. Of the problems of a premature baby, respiratory causes are the most common cause of the admission to NICU. The common respiratory problem is RDS or Hyaline membrane disease (HMD), whose incidence is higher in preterms [2]. Surfactant therapy is becoming increasingly common for such cases. Though the first official report of the beneficial use of surfactant therapy in neonates with RDS was published in 1980 [6], there are very few studies describing outcomes and effects of surfactant therapy in preterm VLBW neonates. Data on survival and morbidity of VLBW neonates are mostly from the developed countries and suggests a significant decline in mortality in last years [7]. However, similar information is lacking from developing countries. Thus present study aimed to describe the morbidity and mortality profile of surfactant therapy in preterm VLBW neonates.

MATERIAL AND METHODS:

The present study was a single centric, hospital based observational study, conducted at Sir Padampat Institute of Neonatology and Paediatric Health (S.P.I.N.P.H.), S.M.S Medical College, Jaipur, Rajasthan. It is one of the largest tertiary referral centre of North-West India. The study was carried out over a period of from July 2021 to November 2022. The study included 110 Preterm VLBW neonates with RDS (based on clinical /x ray chest findings) who were admitted and given Surfactant in NICU during the study period. Study included Preterm VLBW neonates from 28 to 34 weeks of gestation and from 500gms - 1500gms of birth weight with RDS were enrolled. Neonates were recruited consecutively till sample size was achieved and Preterm neonates with severe congenital malformations and chromosomal defects were excluded from the study.

Sample size was calculated at 95% confidence level and 10% allowable error expecting 26.7% mortality among VLBW neonates after the administration of surfactant therapy [8]. Sample size was calculated to be a minimum of 75, which was increased considering attrition.

Sample size was calculated using the formula

$$n = Z\alpha^2 pq/L^2,$$

After inclusion in the study detailed clinico-epidemiological informations were gathered by interviewing the parents/ attendants and were recorded in a pre designed semi- structured Study Performa. Information was collected regarding Maternal and Fetal parameters under Pre-natal, Natal and Post-natal History. Maternal factors included basic details like name, age, weight, gravida, parity, consanguinity, abortions and complications if any during pregnancy. Fetal factors included Birth weight, time, place of birth and admission, Gestational age, Apgar score, surfactant details, complications if any and outcome. For the assessment of Respiratory distress in VLBW neonates, Silverman scoring was done. The surfactant (dose 4ml/kg) was administered intratracheally according to standard procedures in four divided aliquots via either INSURE (Intubate, Surfactant administration and Extubation) to bubble CPAP technique or LISA (Least Invasive Surfactant Administration).

Statistical Analysis:

Quantitative variables were expressed as mean and standard deviation while qualitative variables were expressed as proportion. Difference between proportions was tested by chi square test / Fisher's exact test. A p value less than 0.05 was considered statistically significant. All

statistical analysis was done using Epi info version 7.2.1.0 statistical software.

Ethical Aspect:
Ethical clearance was obtained from Institutional Ethics Committee prior to initiation of study. Written informed consent was obtained from parents or legally acceptable representatives of all subjects prior to inclusion in the study. Confidentiality, privacy and safety of study participants were ensured at all stages of the study period.

Observations:
Table 1 : Neonatal characteristics

Parameters	Variables	Number (No.)	Percentage (%)
Gender	Male	67	60.9
	Female	43	39
Birth weight (grams)	500-749	13	11.8
	750-999	20	18.1
	1000-1249	46	41.8
	1250-1500	31	28.1
Gestational age (weeks)	<28 wks	10	9
	28-30 wks	16	14.5
	30-32 wks	36	32.7
	32-34 wks	44	40
	>34 wks	4	3.6
Mode of delivery	LSCS	19	17.2
	NVD	91	82.7
Immediate cry after birth	No	33	30
	Yes	77	70
Age of mother (years)	<20 years	10	9
	21- 30 years	77	70
	>30 years	23	20.9
Gravida	G1	44	40
	G2	41	37.2
	G3 or more	25	22.6
Antenatal steroids	No	102	92.7
	Yes	8	7.3
Antenatal complications	Anaemia	19	17.2
	APH	27	24.5
	GDM	5	4.5
	PIH	4	3.6
	Oligohydramnios	20	18.1

Out of 110 study participants, 67 (60.9%) were Males and 43 (39%) were Females. Majority (41.8%) Neonates had Birth weight 1000 to 1249 gm, and 44 (40%) Neonates had GA between 32-34 weeks, 36 (32.7%) had GA between 30-32 weeks.

Majority (82.7%) delivered by NVD and 19 (17.2%) had LSCS. Nearly one third (30%) had history of Delayed cry after birth. Majority of mothers (40%) were primigravida. Only 8 (7.3%) had taken Antenatal steroids. Half of mothers had antenatal Complications including APH, anemia, GDM and PIH (Table 1).

Table 2: Admission Characteristics of Patients

Parameters	Variables	Number (n)	Percentage
Age at admission	LH <2	3	2.7
	LH 2-6	62	56.3
	LH 6-12	23	20.9
	LH 12-24	16	14.5
	LH > 24	6	5.4
Already received surfactant	NO	97	88.1
	YES	13	11.8
If Yes, No. of doses	1	10	9.0
	2	3	2.7
	3	0	0
SAS score	SAS <3	1	0.9
	SAS 3-6	83	75.4
	SAS >6	26	23.6
Technique of surfactant delivery	INSURE	42	38.1
	LISA	68	61.8
Type	Prophylactic	27	24.5
	Rescue	83	75.4
	Early rescue	3	2.7
	Late rescue	80	72.7
Repeat dose	No	86	78.1
	Yes	24	21.8
If yes, number of doses	1	19	17.2
	2	3	2.7
	3	2	1.8

Most neonates (56.3%) were admitted between LH_2 to LH_6. Only 13 (11.8%) neonates had already received surfactant before admission. Majority of neonates (40.9%) had SAS score of 5 on admission, 17.2% neonates had SAS scoring of 4, and 17.2% neonates had SAS scoring of 6. Majority of neonates (61.8%) were given surfactant via LISA, and 24 (21.8%) were given repeat dose of surfactant (Table 2).

Table 3: Outcome characteristics of study subjects

Parameters	Variables	Number	Percentage
Duration of Hospital Stay	<3 days	14	12.7
	3-6 days	24	21.8
	7-10 days	63	57.2
	≥10 days	9	8.1
Complications	Apnoea	32	29
	PVL	10	9
	ROP	8	7.2
	Septicaemia	65	59
	Shock	14	12.7
	BPD	1	0.9
	NEC	2	1.8
	Pulmonary haemorrhage	7	6.3
	PDA	1	0.9
Final outcome	Expired	22	20
	Survived	88	80

Duration of Hospital stay was found that maximum from 7-10 days (57.2%). Septicemia (59%), Apnea (20%) and Shock (12.7%) were the major complications. In hospital mortality occurred in 22 (20%) neonates even after giving surfactant (Table 3).

Table 4 : Factors associated with mortality

		Death		Survived		P value
		N	%	N	%	
Gender	Males	15	68.1	52	59	0.434
	Females	7	31.8	36	40.9	
Gestational age	< 28 wks	7	31.8	4	4.5	0.293
	28-30 wks	6	27.2	11	12.5	
	30-32 wks	5	22.7	29	32.9	
	32-34 wks	4	18.6	40	45.4	
	>34 wks	0	0.0	4	4.5	
Birth weight (gm)	500-749	6	27.2	6	6.8	0.002
	750-999	9	40.9	14	15.9	
	1000-1249	7	31.8	37	42	
	1250-1500	0	0.0	31	34	
SAS score on admission	<3	0	0	1	1.1	<0.001
	3-6	6	27.2	77	87.5	
	>6	16	72.7	10	11.3	
Immediate cry after birth	No	16	72.7	17	19.3	<0.001
	Yes	6	27.2	71	80.6	
Age at Admission	LH<2	0	0	3	3.4	0.574
	LH 2-6	14	63.6	48	54.5	
	LH 6-12	6	27.2	17	19.3	
	LH 12-24	1	4.5	15	17	
	LH >24	1	4.5	5	5.6	
type of surfactant administration	Prophylactic	6	27.2	21	23.8	0.780
	Early rescue	1	4.5	2	2.2	
	Late rescue	15	68.1	65	73.8	
Technique of surfactant administration	LISA	4	18.1	64	72.7	<0.001
	INSURE	18	81.8	24	27.2	
Repeat dose	No	7	6.3	76	69	<0.001
	Yes	13	11.8	14	12.7	

Lower birth weight, High SAS score at admission, no immediate cry after birth, Insure technique of surfactant application and need for repeat dose of surfactant were significantly associated with higher mortality (Table 4).

DISCUSSION:
In Premature babies, anatomically immature lungs and lack of

pulmonary surfactant are the main causes of RDS. Early administration of surfactant is indicated for very preterm neonates whose mothers did not receive antenatal corticosteroids and for preterm infants who requires intubation [9]. Studies have shown that surfactant replacement is linked to improved survival [10]. The present study analyzed the outcomes of surfactant therapy in 110 preterm VLBW neonates who were admitted with RDS.

Majority of neonates (56.3%) were admitted between LH_2 to LH_6 and only 3 (2.7%) neonates were admitted at LH<2. In a similar study by, **Bhutta Z. A. et al** observed that most neonates with RDS were admitted between LH_3 to LH_6 and 22% neonates had already received surfactant before admission [11]. In the present study, 75.4% neonates were given rescue therapy and 24.5% were given surfactant prophylactically. **Hameed NN et al** reported that majority (42.4%) neonates received prophylactic surfactant, 35.6% neonates received early rescue and 22.1% neonates received late rescue surfactant [12]. Recent guidelines advise the administration of surfactant as early rescue therapy [9]. Most neonates (57.2%) stayed in hospital from 7-10 days. Similarly, **Hameed NN et al** also observed that hospital stay ranged between 7-8 days [12].

In our study, Septicemia (59%), Apnea (29%) and Shock (12.7%) were the major complications. Past studies have reported Sepsis as the most prevalent consequence [12-14]. **Keskar U S et al** reported RDS in 46.15%, neonatal sepsis in 19.23% and PDA in 16.66% babies [15]. **Tyagi A et al** observed that septicemia and PDA were the most common complications followed by early-onset sepsis, birth asphyxia, prematurity, RDS, and meconium aspiration syndrome [16]. **Kumar S. et al** observed that the major cause of morbidity was neonatal sepsis (25%), prematurity (19%), neonatal jaundice (18%), birth asphyxia (5 %) [17].

In our study mortality occurred in 22 (20%) patients even after giving surfactant. Babies who required mechanical ventilation (SAS >7, APGAR <3) had higher mortality rate as compared to those who required CPAP (SAS 3-6, APGAR 3-6) and Oxygen by nasal prongs (SAS <3, APGAR>6). **Manandhar SR et al** in a similar study reported mortality rate of 26.7% among preterm infants with HMD getting Surfactant replacement therapy [8]. **Greiner E. et al** in a study determining the outcome of infants presenting with persistent RDS observed that Infant mortality increased after receiving two doses of surfactant and with Mechanical ventilation than CPAP [18].

In our study higher mortality was associated with low gestational age and low birth weight. Similar study by **Manandhar SR et al** observed that lower birth weights (<1200g) and low gestational ages (< 30 weeks) were associated with the highest mortality [8]. **Pacifici GM et al** reported that surfactants can reduce infant mortality by upto half in gestational age under 30 weeks, birth weight 1120 – 1240gms and gestational ages of 30-34 weeks [19]. In present study highest risk of morbidity of was observed in neonates with SAS score of >6 on admission. **Bhutta Z A et al** observed a significantly greater risk of morbidity with lower Apgar scores of <7 and higher SAS score of >5. In our study Mortality was higher in neonates with birth asphyxia / delayed cry at birth [11]. Similar results were obtained by **Bhutta Z A et al** that observed significantly greater risk of mortality of 70% neonates with birth asphyxia [11].

Antenatal steroids are well known to reduce mortality as well as various morbidities of preterm infants [4]. In the present study only 7.3% received antenatal steroids. It was found that the mortality was higher in neonates who had not received antenatal steroids, as was similarly reported by **Isayama T et al** in VLBW neonates [20]. In present study, higher mortality was observed with late rescue surfactant administration. **Hameed NN et al** observed that Infants who received prophylactic surfactant had the highest case fatality rate [12]. **Pattar M et al** observed that mortality was less in the early rescue surfactant group (28.94%) than in non-surfactant group (54.92%) [14]. However, the late neonatal death was more in the prophylactic surfactant group (63.63%) than in non-surfactant group (53.84%). Various studies have reported early rescue surfactant therapy to significantly reduces mortality and respiratory morbidity [21-23]. In present study mortality was higher in neonates requiring repeat dose of surfactant, as has been similarly reported by other studies [18,24].

CONCLUSION

Present study highlights the positive impact of surfactant therapy in very low birth weight preterm newborns. The use of surfactant therapy improved the survival outcome and decreased the associated morbidities with respiratory distress syndrome. Highest survival benefit was seen among the VLBW newborns with birth weight >1000 grams, Gestational age between 32- 34 weeks, Silverman Anderson score of >6 at the time of admission, Apgar score of 3-6 and who were managed timely by giving surfactant. Despite its widespread use, the optimal method of surfactant administration and its outcome, effects in preterm infants has yet to be clearly determined. Further clinical studies with multi-centric designs and varying dose and timing of surfactant therapy could help optimize the management and outcome of very low birth weight newborns.

Conflict of Interest: Nil

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