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Outcome of Early Versus Late Surfactant Therapy in Preterm Neonates with Respiratory Distress Syndrome at a Tertiary Care Centre

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Abstract

Background: Respiratory distress syndrome (RDS) or hyaline membrane disease (HMD), has been recognized as the most common co-morbidity of prematurity. Prematurity and RDS largely contribute to early neonatal morbidity and mortality. With adequate antenatal steroid and early continuous positive airway pressure, early surfactant therapy improve survival outcome. **Material & Methods:** Prospective interventional study included newborns with prematurity 28-36 weeks(GA) with clinical Respiratory distress syndrome and birth weight(BW)>650 gm. All subjects were preferably provided early surfactant therapy (within 2hours after birth). Surfactant (survanta) was delivered by INSURE technique (Intubate- Surfactant administration- Extubate) and only those who required further respiratory support were ventilated. Records on birth weight, gestational age, timing of therapy (early/late), sepsis, complications, and survival/death outcome were collected and data was analyzed using SSPS version 20 software. **Results:** Out of 76 neonates (42 male, 34 female), 46 received early surfactant therapy and 30 obtained it late; Although mortality was observed with both early(36.66%) and late therapy(63.33%), there was significantly higher survival with early therapy. higher mortality occurred in lower Birth weight(LBW) /Gestational age (GA) subgroups. Culture positive sepsis was found in 52.6% with higher association with late therapy . Hypotension was most common complication with late intervention , whereas there was no difference for pulmonary haemorrhage or apnea. **Conclusion:** Early surfactant administration improved survival with minimal complications in RDS except for extremely

Keywords:- Preterm neonates, RDS, Surfactant therapy, Early administration, Survival outcome.

INTRODUCTION

In developing countries, neonatal mortality account for more than one third of under five mortality with higher deaths occurring in the early neonatal period i.e. 25%–45% occurring in the first 24 hours, and about 75% during the first

week of life.[1,2] (RDS) or hyaline membrane disease (HMD), has been recognized as the most common co-morbidity of prematurity.

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Surfactant replacement had been established as an effective and safe therapy for immaturity-related surfactant deficiency by the early 1990s.[3,4] The first clinical use of exogenous surfactant to treat RDS was by Fujiwara and colleagues in 1980.[5] From the 1990s onwards, several artificial surfactants have been produced commercially around the world as standard therapy for RDS.[4,5,6,7,8]

Although exogenous surfactant administration has its own known complications like hypotension or worsening shock, apnea, bradycardia, pneumothorax, PIE (pulmonary interstitial emphysema) and pulmonary hemorrhage, surfactant therapy has been the standard of care in preterm infants with RDS and is associated with a decrease in neonatal mortality, pneumothorax, and increased survival without bronchopulmonary dysplasia (BPD).

Currently natural surfactants from animal origin (bovine/calf, porcine) have emerged as preferred therapeutic agents.[9,10] These have markedly improved the survival of preterm, LBW, and VLBW infants, and have resulted in reduced neonatal and infant mortality.[6] The timing of surfactant administration is also crucial as evidences support better outcomes with early administration in addition to CPAP and preferable noninvasive or lung protective ventilation strategies.[11,12,13,14]

Till date many studies and trials have been done using different surfactant preparations, varying doses/ schedules or delivery methods and on varying subjects of different gestational maturity or birth weight bands. We planned this study to evaluate outcome of early surfactant therapy versus late surfactant therapy.[15,16,17,18]

MATERIAL AND METHODS

Prospective study design was used to study Outcome of surfactant therapy with respect to timing of its administration (i.e. early within two hours of life and late after 2hours), different birth weight and different gestational age. Secondarily to compare complications and association of sepsis with timing of therapy.

This is a hospital based study conducted in NICU (neonatal intensive care unit) at Department of paediatrics Grants government medical college Mumbai, India. Within a time period of One year (June 2021 to June 2022).

After taking ethical clearance from institutional committee, written consent was obtained from parents/ attendants before administration of surfactant in all eligible cases after obtaining detailed history, gestational age and birth details from parents and obstetrical records. All cases were evaluated using Silverman score and other risks for Respiratory distress syndrome to decide giving early prophylactic or rescue therapy.

Surfactant in the form of 'Survanta' was administered by 'INSURE' technique (INtubation -SURfactant administration-Extubation) and only those who needed ventilatory support for various co-morbidities or surfactant related complications were further mechanically ventilated. Overall comparative data on survival/ death outcome (based on early/late therapy, gestational age, and birth weight), improvement on post surfactant RDS score, complications of surfactant therapy, and causal association of

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culture positive/negative sepsis with mortality were recorded.

Inclusion Criteria

1. All babies between 28-30 weeks of gestational age
2. 31-36 weeks babies with clinical RDS

Exclusion Criteria

1. Babies with gestational age <28weeks, >36weeks
2. 31-36 weeks babies without clinical RDS
3. Birth weight< 650gm
4. Major congenital anomalies and parental refusal for consent

RESULTS

Out of 76 preterm newborns enrolled, 42 were male and 34 female. Of those, out of 40 patients receiving early surfactant therapy (within < 2hours of birth) 54% where male and 46% where female, while among 36 late therapy recipients, around 45% were female and 55% were male.

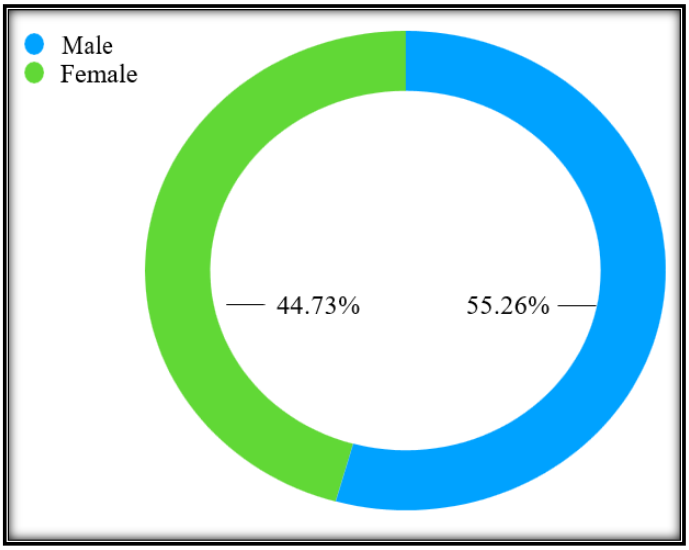

Table 1: Gender distribution of patients in study groups. P- 0.938

			Time of surfactant delivery		Total
			Early	Late	
Gender	Female	Count	15	20	34
		% gender	42.86%	58.82%	44.73%
	Male	Count	26	16	42
		% gender	61.9%	38%	55.26%
Total		Count	40	36	76
		Percent %	52.63%	47.36%	100.0%

Table 2: Outcome after early and late surfactant therapy in different gestational age subgroups (p-0.510, p-0.809)

Gestational age (GA) I Weeks		Outcome					
		Death			Improved		
		Time of surfactant		Total	Time of surfactant		Total
		Early	Late		Early	Late	
	Count	5	11	16	13	7	20
28-30	% within GA	31.25%	68.75%	100%	65%	35%	100%
	Count	6	8	14	16	10	26
31-36	% within GA	42.85%	57.1%	100%	61.53%	38.46%	100%

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Total	Count	11	19	30	29	17	46
	% within GA	36.66%	63.33%	100%	63%	37%	100%

Table 3: Outcome after early and late surfactant therapy in different birth weight sub-groups. (p=0.156, p=0.989)

Birth weight			**Death**			**Improved**		
			Time of surfactant		**Total**	**Time of surfactant**		**Total**
			Early	**Late**		**Early**	**Late**	
Weight (kg)	0.65-1.2	Count	4	12	16	12	7	19
		%within weight	25%	75%	100%	63.15%	36.84%	100%
	>1.2	Count	7	7	14	17	10	27
		%within weight	50%	50%	100%	62.96%	37%	100%
Total		Count	11	19	30	29	17	46
		%within weight	36.66%	63.33%	100%	63%	37%	100%

Overall patient outcome indicated that only 46 babies had survival/Improved after surfactant therapy and 30 died in this study. Significantly more deaths occurred among subjects receiving late surfactant therapy i.e. 19/30 (63.3%) compared to 11/30 deaths (36.6%) among early therapy group. Although no statistically significant difference was obtained for survival and death outcomes between two study groups (based on surfactant timing) with respect to different subgroups of gestational age [Table 2] and birth weight [Table 3].

If we discard poor outcomes of extremely LBW/premature subgroup bands and then compare overall survival benefits, then it definitely reveals significantly favorable outcome with early surfactant therapy. Thus it seems, survival outcome might not be solely dependent on surfactant therapy or its timing of administration, rather being affected by prematurity related other unfavorable risk factors.

A simple observation on subgroup analysis for survival outcome (without comparing with early/late timing of therapy) suggested a clear cut trend of more favorable outcome with both higher birth weight and gestational maturity.

Table 4: Overall survival/death outcomes with respect to different LBW subgroups irrespective of timing of surfactant delivery. (p=0.304)

Birth weight (in grams)	**Improved**	**Death**	**Total**	**Mortality**	**Survival**
650 - 1200	19	16	35	45.7%	54.2%
>1200	27	14	41	34.1%	65.8%
Total	46	30	76		

Table 5: Overall mortality / survival rates among different gestational age subgroups. (P-0.400)

Gestation age (weeks)	**Improved**	**Death**	**Total**	**Mortality**	**Survival**
28-30	20	16	36	44.4%	55.6%
31-36	26	14	40	35.0%	65.0%

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Total	46	30	76		

[Table 4 and 5] reveal significant difference on mortality rates between two birth weight bands 45.7% for 650-1200gm, while 34.1% for 1200 and gestation age subgroups mortality 44.4% in 28-30wks, 35% mortality was seen in 31-36wks.

Together these observations showing overall poor outcome subjects suggest that higher mortality in this study could have occurred due to extreme immaturity and poor birth weight themselves being fatal co- morbid factors, nullifying survival benefit of surfactant irrespective of its timing of administration.

Among our study subjects, total 77.9% babies had features of sepsis with culture positive septicemia documented in 52.6% (40/76), culture negative or only clinical sepsis was found in 22.3% patients (n=17) and only 25% babies (n=19) had no clinical/proven sepsis till their hospital stay [Table 6].

Table 6: Comparison of frequency of sepsis between two study groups. (p value = 0.809)

			Time of surfactant delivery		**Total**
			Early	**Late**	
Sepsis	Absent	count	11	8	19
		%	27.6%	22.2%	25%
	Culture +ve	count	21	19	40
		%	52.5%	52.7%	52.6%
	Culture -ve	count	8	9	17
		%	20%	25%	22.3%
Total		count	40	36	76
		%	52.6%	47.36%	100%

On comparing association of sepsis between study groups, we found higher occurrence of sepsis in patients receiving early surfactant therapy i.e. in early therapy group 40/76 (52.6%) had sepsis, while after late therapy 36/76 (47.36%) subjects had sepsis. Sepsis was culture proven in 52.7% (19/40) of late therapy recipients and about 52.5% (21/40)septic babies were from early treatment group. Among immediate complications encountered in our study, 19.7% patients suffered pulmonary haemorrhage, 32.8% had hypotension and 11.8% had apnea [Table 7].

Table 7: Comparison of complications in two study groups. (p=0.291, 0.523, 0.568)

Complications		**Time of surfactant delivery**		**Total**
		Early	**Late**	
Hypotension	Count	11/40	14/36	25
	%	27.5%	38.8%	32.8%
Pulmonary haemorrhage	Count	9/40	6/36	15
	%	22.5%	16.6%	19.7%
Apnea	Count	5/40	4/36	9
	%	12.5%	11.1%	11.8%

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Significant association was found only for hypotension with late timing of surfactant therapy as with late therapy 14/36 (38.8%), 11/40(27.5%) patients developed hypotension in early therapy, whereas there was no significant association of pulmonary haemorrhage and apnea with timing of surfactant administration.

DISCUSSION

Our study primarily aimed at evaluating survival benefits of early surfactant administration in a public sector tertiary setting with resource constraints and multiple risk factors for mortality in addition to prematurity with RDS alone. Secondarily, one major objective was to compare mortality between different birthweight and gestational prematurity subgroups with reference to timing (early/late) of single dose surfactant administration.[19]

A total of 76 neonates between 28-36 weeks of gestational age and birth weight >650gm with clinical features/risks of RDS had been enrolled, of which 42 were male and 34 were female. 46 neonates received early therapy and 30 could be given late surfactant therapy. With respect to primary outcome our study showed comparatively higher survival rate in patients receiving early surfactant therapy compared to late rescue therapy (63% vs 37%) and with higher mortality after delayed rescue therapy compared to early surfactant therapy (63.33% vs 36.66%).[20,21]

Another important observation in our study was significant difference on mortality rates between two birth weight bands for 53.33% 650-1200gm ,while 46.66% for 1200 and for gestation age subgroups mortality 53.33% in 28-30wks, 46.66% mortality was seen in 31-36wks. Such observations in our study subjects suggest that higher mortality can occur due to extreme prematurity and poor birth weight themselves being fatal co morbid factors, altering benefit of surfactant even if early instituted.[22,23]

In our study total 77.9% babies had features of sepsis with culture positive septicemia documented in 52.6% (40/76), culture negative or only clinical sepsis was found in 17% patients (n=17) and only 25% babies (n=19) had no sepsis. we found higher occurrence of sepsis in patients receiving early surfactant therapy i.e. in early therapy group 40/76 (52.6%) had sepsis, while after late therapy 36/76(47.36%) subjects had sepsis. Sepsis was culture proven in 52.7% (19/40) of late therapy recipients and about 52.5% septic babies were from early treatment group.

Among complications, hypotension or worsening shock was more frequently encountered in subjects receiving late surfactant therapy, whereas no significant difference was noted between study groups for pulmonary haemorrhage and apnea . None of our subjects developed pneumothorax or air leak syndrome. Similarly decreased risk of pneumothorax and pulmonary interstitial emphysema and chronic lung disease with less overall complications in early group was observed by many studies/reviews, although incidence of pneumothorax was similar with early and late therapy in few studies.[24,25]

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CONCLUSIONS

Early surfactant administration in our study showed improved outcome with higher survival benefit compared to late therapy in preterm neonates with RDS, although among extreme premature/ELBW babies, there was higher mortality irrespective of timing of surfactant therapy. In terms of complications, hypotension occurred more frequently after late therapy while pulmonary haemorrhage and apnea had similar occurrence with both early and late therapy.

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