

Comparison of survival outcome in early versus late surfactant therapy in preterm neonates with respiratory distress syndrome at a tertiary care centre: A randomized control trial (Open)

Phuljhele S.¹, Rathia S.K.², Chukkanakal J.K.³

¹Dr. Sharja Phuljhele, Professor and Head, ²Dr. Santosh Kumar Rathia, Assistant Professor; ³Dr. Jitendra K Chukkanakal, Junior Resident (PG student), all authors are affiliated to Department of Pediatrics, Pt. J. N. M. Medical College, Raipur, CG, India.

Address for Correspondence: Dr. Santosh Kumar Rathia, Email: drsantoshrathia84@gmail.com

Abstract

Introduction: Prematurity and RDS largely contribute to early neonatal morbidity and mortality. With adequate antenatal steroid and early CPAP, early surfactant therapy improve survival outcome. **Material and Methods:** Prospective interventional study included newborns with 24-28 weeks prematurity or 28-34 weeks(GA) with clinical RDS and birth weight(BW)>650gms. All subjects were preferably provided early surfactant therapy (within 2hours after birth). Surfactant (Curosurf) 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), duration of ventilation, sepsis, complications, and survival/death outcome were collected and data was analysed using SSPS version 17. **Results:** Out of 100 neonates (49 male, 51 female), 46 received early surfactant therapy and 54 obtained it late; significantly more indoor patients could be treated early ($p<0.0001$). Although high mortality was observed with both early (65.2%) and late therapy (85.2%), there was significantly higher survival with early therapy ($p=0.018$). Though no statistical differences of outcome were observed with different GA and BW in study groups; irrespective of timing of therapy, higher mortality occurred in lower BW/GA subgroups with least survival among extremely preterms <27 wks ($p=0.000057$) and ELBW <1000 gm($p=0.013$). No difference was seen for need of re-intubation/ventilation, but duration of ventilation was more on late group ($p=0.043$). Culture positive sepsis was found in 68% with higher association with late therapy ($p=0.033$). Hypotension was frequent complication with late intervention ($p=0.029$), whereas there was no difference for pulmonary hemorrhage or apnea. **Conclusion:** Early surfactant administration improved survival with minimal complications in RDS except for extremely premature/LBW babies.

Key words: 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 [1] with higher deaths occurring in the early neonatal period i.e. 25%–45% occurring in the first 24 hours, and about 75% during the first week of life [1,2]. Respiratory distress syndrome (RDS) or hyaline membrane disease (HMD), has been recognized as the most common co-morbidity of prematurity. Over half of those with extreme/very

low birth weight (between 500-1500 grams) show clinical signs of RDS as well [3, 4]. Same time it poses the commonest indication for ventilation in neonates in India [5-7]. Surfactant replacement had been established as an effective and safe therapy for immaturity-related surfactant deficiency by the early 1990s [8]. The first clinical use of exogenous surfactant to treat RDS was by Fujiwara and colleagues in 1980[9]. From the 1990s onwards, several artificial surfactants have been produced commercially around the world as standard therapy for RDS [8-12]. Although exogenous surfactant

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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 [13,14]. They are available in market with different brands with varying dose/concentrations and cost.

These have markedly improved the survival of preterm, LBW, and VLBW infants, and have resulted in reduced neonatal and infant mortality [10]. The timing of surfactant administration is also crucial as evidences support better outcomes with early administration [13,15–26] in addition to CPAP and preferable noninvasive or lung protective ventilation strategies [7,16,22,26].

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 [13,14,25–28]. We planned this study to evaluate practical benefits of early surfactant therapy in wider possible subject groups including even most premature babies with extremely LBW i.e. even so called micropremies <800gms, and that too in a setting with certain limitations and resource constraints with regards to ideal neonatal care facilities.

Materials and Methods

Objectives: To compare survival 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. Secondly to compare need of mechanical ventilation, complications and association of sepsis with timing of therapy

Study design- Prospective interventional study (Randomized clinical trial, open)

Study setting- NICU (neonatal intensive care unit) at Pt JNM Medical College and Dr BR Ambedkar Hospital, Raipur, CG, India.

Study Period – One year (October 2015 to October 2016)

Participants: Inclusion criteria

1. All babies between 24-28 weeks of gestational age
2. 28-34 weeks babies with clinical RDS

Exclusion criteria

1. Babies with gestational age <24 weeks, >34weeks
2. 28-34 weeks babies without clinical RDS
3. Birth weight<650gms
4. Major congenital anomalies and parental refusal for consent

Process of selection of intervention and subject allocation:

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 Silvermann score and other risks for Respiratory distress syndrome to decide giving early prophylactic or rescue therapy, although majority of patients were randomly allocated for late therapy by default (due to major burden of outborn and delayed admissions in our NICU).

Surfactant in the form of ‘Curosurf’ 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, need and duration of further ventilation, complications of surfactant therapy, and causal association of culture positive/negative sepsis with mortality were recorded.

Statistical analysis

- Data collected on Microsoft excel sheet was interpreted and expressed as percentage and mean \pm S.D.
- Kolmogorove-Smirnove analysis was performed for checking linearity of the data.

- Fischer's exact test or Chi square test was used to analyze the significance of difference between frequency distribution of the data.
- Students unpaired t test was used to assess the significance of difference between two means.
- P value <0.05 was considered as statistically significant.
- SPSS© for windows™ Vs 17, IBM™ Corp NY and Microsoft excel™ 2007, Microsoft® Inc USA was used perform the statistical analysis.

Results

Out of 100 preterm newborns enrolled, 49 were male and 51 female. Of those, out of 46 patients receiving early surfactant therapy (within < 2hours of birth), male and female were equal; while among 54 late therapy recipients, around 52% were female and 48% were male.

Table 1: Gender distribution of patients in study groups.

			Time of surfactant delivery		Total	P value
			EARLY	LATE		
Gender	FEMALE	Count	23	28	51	0.50
		% within	50.0%	51.9%	51.0%	
	MALE	Count	23	26	49	
		% within	50.0%	48.1%	49.0%	
Total		Count	46	54	100	
		% within	100.0%	100.0%	100.0%	

(Chi square test suggests the two study groups were matched for gender (i.e. with non-significant p=0.50).

A total of hundred eligible preterms between 24-34 weeks gestational age and birth weight above 650grams those having risks or clinical features of RDS. On Chi square and t tests, the two study groups were found matched in terms of patient distribution based on both gestational age and birth weight {table 2}.

Table 2: Group statistics showing controlled matching of subjects in two study arms with respect to birth weight and gestational age.

	Surfactant delivery	n= number	Mean	Std. Deviation	Std. Error Mean	P value.
Weight (Kg)	Early	46	1.1928	0.35787	0.05277	0.825
	Late	54	1.1787	0.27772	0.03779	
Gestational age (Weeks)	Early	46	29.9783	2.65405	0.39132	0.676
	Late	54	29.7593	2.55458	0.34763	

On comparing the type of admission (intra/extra-mural) with time of surfactant delivery, we found significantly higher frequency of early administration of surfactant among indoor subjects likely due to timely feasible prophylaxis or rescue therapy. Out of 46 patients in early group 44(95.6%) were inborn and only 2(4.4%) were outborn, while in late therapy group, 96.3% (n=52) were out bourn babies (p<0.0001).

Overall patient outcome indicated that only 24 babies had intact survival after surfactant therapy and 76 succumbed (to RDS and/or other co-morbidities) in this study. Significantly more deaths occurred among subjects receiving late surfactant therapy i.e. 46/76 (60.5%) compared to 30 of total 76 deaths (39.5%) among early therapy group (p=0.018). 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 (p=0.30){see table 3} and birth weight (p=0.40) {table 4}.

Table 3: Outcome after early and late surfactant therapy in different gestational age sub-groups (P value=0.3).

Gestational age		Outcome					
		Death			Improved		
		Time of surfactant delivery		Total	Time of surfactant delivery		Total
		Early	Late		Early	Late	
	Count	10	6	16	0	0	0
24-27	% within Gestational age (Weeks)	60.0%	40.0%	100.0%	0.0%	0.0%	0.0%
	Count	12	28	40	5	1	6
28-30	% within Gestational age (Weeks)	30.0%	70.0%	100.0%	83.3%	16.7%	100.0%
	Count	9	11	20	11	7	18
31-34	% within Gestational age (Weeks)	45.0%	55.0%	100.0%	61.1%	38.9%	100.0%
Total	Count	30	46	76	16	8	24
	% within Gestational age (Weeks)	39.5%	60.5%	100.0%	66.7%	33.3%	100.0%

Table 4: Outcome after early and late surfactant therapy in different birth weight sub-groups (P value=0.40).

			Death			Improved		
			Time of surfactant delivery		Total	Time of surfactant delivery		Total
			Early	Late		Early	Late	
Weight (Kg)	0.650-0.850	Count	9	7	16	1	1	2
		% within Weight (Kg)	56.2%	43.8%	100.0%	50.0%	50.0%	100.0%
	0.851-1.0	Count	4	7	11	3	0	3
		% within Weight (Kg)	36.4%	63.6%	100.0%	100.0%	.0%	100.0%
	1.01-1.2	Count	6	15	21	0	1	1
		% within Weight (Kg)	28.6%	71.4%	100.0%	.0%	100.0%	100.0%
	1.21-1.5	Count	10	13	23	7	5	12
		% within Weight (Kg)	43.5%	56.5%	100.0%	58.3%	41.7%	100.0%
	>1.5	Count	1	4	5	5	1	6
		% within Weight (Kg)	20.0%	80.0%	100.0%	83.3%	16.7%	100.0%
	Total	Count	30	46	76	16	8	24
		% within Weight (Kg)	39.5%	60.5%	100.0%	66.7%	33.3%	100.0%

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 5: Overall survival/death outcomes with respect to different LBW subgroups irrespective of timing of surfactant delivery.

Birth Weight (in grams)	IMPROVED (n)	DEATH (n)	TOTAL (n)	Mortality (%)	Survival (%)
650-850	2	16	18	88.9%	11.1%
851-1000	2	11	13	84.6%	15.4%
1001-1200	3	19	22	86.4%	13.6%
1201-1500	15	20	35	57.1%	42.9%
>1500	6	6	12	50.0%	50.0%
TOTAL	28	72	100	-	-

(P value = 0.013)

Table 6: Overall mortality / survival rates among different gestational age subgroups.

Gestational Age (Weeks)	Improved (N)	Death (N)	Total (N)	Mortality (%)	Survival (%)
25-27	0	17	17	100%	0%
28-30	6	39	45	86.7%	13.3%
31-34	18	20	38	52.6%	47.4%
TOTAL	24	76	100	-	-

(P value = 0.00005)

Table 5 and 6 reveal significant difference on mortality rates between various birth weight bands {85-89% for 650-1200gms, while 50-57% for >1200 gms; p=0.013} and gestation age subgroups {all died with 24-27 weeks prematurity, while less mortality(86.7%) in 28-30wks, and least 52.6% was seen in 31-34wks maturity groups; p=0.00005}.

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.

Out of 100 subjects, 84(84%) required ventilation and 16(16%) did not. There was no significant difference noted between two groups with reference to need for ventilation post surfactant therapy (p=0.266) i.e. out of 46 patients in early therapy, 37(80.4%) required ventilation and out of 54 patients in late therapy, 47(87%) required ventilation. But, significant difference was found for total duration of ventilation with average duration of ventilation 1.72 days in late therapy group and 1.56 days in early group (p=0.043){see table 7}.

Table 7: Comparison of Duration of ventilation between study groups.

			Time of surfactant delivery		Total	P value
			EARLY	LATE		
Duration of ventilation	Absent	Count	9	7	16	0.043
		%	19.6%	13.0%	16.0%	
	<1	Count	3	3	6	
		%	6.5%	5.6%	6.0%	
	1-3	Count	34	38	72	
		%	73.9%	70.4%	72.0%	
>3	Count	0	6	6		
	%	.0%	11.1%	6.0%		
Total		Count	46	54	100	
		%	100.0%	100.0%	100.0%	

Among our study subjects, total 77% babies had features of sepsis with culture positive septicemia documented in 68 % (68/100), culture negative or only clinical sepsis was found in 9% patients (n=9) and only 23% babies (n=23) had no clinical/proven sepsis till their hospital stay {table 8}.

Table 8: Comparison of frequency of sepsis between two study groups.

			Time of surfactant delivery		Total	P value
			EARLY	LATE		
Sepsis	Absent	Count	16	7	23	0.033
		%	34.8%	13.0%	23.0%	
	Culture +ve	Count	26	42	68	
		%	56.5%	77.8%	68.0%	
	Culture -ve	Count	4	5	9	
		%	8.7%	9.3%	9.0%	
Total		Count	46	54	100	
		%	100.0%	100.0%	100.0%	

On comparing association of sepsis between study groups, we found higher occurrence/coexistence of sepsis (overall both clinical/proven) in patients receiving late surfactant therapy (p=0.033) i.e. in late therapy group 47/54 (87%) had sepsis, while after early therapy 30/46 (65.2%) subjects had/developed sepsis.

Sepsis was culture proven in 62% (42/68) of late therapy recipients and about 38% septic babies were from early treatment group.

Among immediate complications encountered in our study, 15% patients suffered pulmonary hemorrhage, 30% had hypotension and 11% had apnea {see table 9}.

None of our subjects developed pneumothorax or pulmonary interstitial emphysema/air-leak syndrome.

Table 9: Comparison of complications in two study groups.

Complications		Time of surfactant delivery		Total	P value
		Early	Late		
Hypotension	Count	9/46	21/54	30	0.029
	(%)	19.6%	38.9%	30.0%	
Pulmonary hemorrhage	Count	7/46	8/54	15	0.587
	(%)	15.2%	14.8%	15.0%	
Apnea	Count	6/46	5/54	11	0.387
	(%)	13.0%	9.3%	11.0%	

Significant association was found only for hypotension with late timing of surfactant therapy as with late therapy 21/54(38.9%) patients developed hypotension/worsening shock compared to 9(19.5%) in early therapy ($p=0.029$), whereas there was no significant association of pulmonary hemorrhage ($p=0.58$) and apnea ($p=0.38$) with timing of surfactant administration.

Discussion

Respiratory distress syndrome has been recognized as the most common co-morbidity of prematurity. Surfactant replacement had been an established effective and safe therapy for prematurity-related surfactant deficiency by the early 1990s and it has also been proven by more recent studies worldwide [7,16,22,26]. Similarly few studies have compared early versus late surfactant administration timing and proven benefits of early over late therapy in terms of less mortality and immediate or late morbidity/complications [13,15–26]. Based on similar observations, 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. Secondly, 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. Additionally, immediate complications, need of mechanical ventilation and association of sepsis were found as major confounding risks of poor outcome in our study.

A total of 100 neonates between 24-34 weeks of gestational age and birth weight >650gms with clinical features/risks of RDS had been enrolled, of which 49 were male and 51 were female. 46 neonates received early therapy and 54 could be given late surfactant therapy with significantly higher frequency of early surfactant administration feasible in indoor patients ($p<0.0001$).

With respect to primary outcome our study showed comparatively higher survival rate in patients receiving early surfactant therapy compared to late rescue therapy (34.8% vs 14.8%, p value =0.018) and vice versa for the mortality rates with higher mortality after delayed intervention (85% vs 65%) {see table 10}.

Table 10: The comparison of our study with other relevant studies.

Comparison with other studies	our study	Jayachandra et al [23]	Hemasree K et al [22]	Sung Mi Kim et al [24]
Patient distribution based on timing of surfactant administration				
early therapy (<2 hours)	46	34	48.4	49.2
Late rescue treatment (>2 hours)	54	66	51.6	50.8
Outcome after early surfactant				
Survival (%)	34.8	71.5	87.8	80.1
Death(%)	65.2	28.5	12.2	19.9
Outcome after late rescue therapy				
Survival(%)	14.8	53.7	86.1	77.5
Death(%)	85.2	46.3	13.9	22.5

Above table depicts comparison of our study with other relevant studies in terms of distribution of subjects according to timing of surfactant administration (early or late) and primary outcome measures (survival or death after early or late therapy)

Although above comparison revealed higher mortality in both early and late therapy groups in our study when compared to other studies (those wouldn't have included extremely low birth weight or preterm/micro preemie babies), but there is statistically significant higher survival with early surfactant therapy when compared to late therapy in our institutional observation (p value=0.018). Similar findings suggesting improved survival with early rescue therapy have been observed by multiple meta-analyses published yet [17,20,21]. Few other previous studies also had shown decreased mortality rates after early surfactant therapy compared to delayed interventions [15,18,19,27]. Another two more studies on outcome of selective late rescue treatment also revealed high mortality (40-50%) probably due to delay in surfactant delivery [16,26]. Even higher mortality (about 85%) was noticed after late therapy in our study, but it was definitely lesser in early therapy group (65%) indicating definite survival benefit of early intervention.

Another important observation in our study was significant difference on mortality rates between various birth weight {85-89% for BW bands 650-1200gms, while 50-57% for >1200 gms; $p=0.013$ } and gestation age subgroups {all died with 24-27 weeks prematurity, while less mortality(86.7%) occurred in 28-30wks, and least 52.6% seen in 31-34wks maturity groups; $p=0.00005$ } with vice versa impression of least survival among extremely preterm (0, 13.3%, and 47.4% survival for <27wk, 28-30wk and 31-34wk GA respectively) and ELBW babies (only 11-15.4% survived in 650-1200 gms subgroups, while overall 43-50% survival was observed for >1200-1500gms subjects) irrespective of timing of surfactant therapy. 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.

Regarding need of ventilation, out of 100 neonates, 84 required mechanical ventilation post surfactant therapy beyond INSURE method of surfactant administration and 16 maintained well on minimal nasal CPAP support with /without oxygen for 6-24 hours. Significant difference was found between early versus late therapy with respect to duration of ventilation ($p=0.043$), but there was no statistically significant difference in terms of immediate need of re-intubation and mechanical ventilation in two study groups (80.4 vs 87.0%, p value=0.266). Previous two studies by Jayachandra et al and Kandraj et al have revealed higher need of mechanical ventilation after late rescue therapy compared to early interventions (31.6% vs 16.2%, and, 52.6% vs 28.5% respectively) [22,23].

On comparing mean duration of further ventilation, we found it to be 37.5 hours after early therapy and 41.3 hrs after late rescue treatment group, while Jayachandra et al had shown similar pattern with lesser mean duration of ventilation in early therapy (42.5 hours against 59 hours in late therapy) [23]. Similarly significant reduction in duration of ventilation in early group compared to late therapy was revealed by many researchers [21,22,29]. Mohamed Garib et al concluded that early administration of surfactant is associated with early extubation and had a lower chance for re-intubation, less duration of total oxygen administration and less hospital stay as well [28]. Swarnkar et al found that implementation of early rescue administration of surfactant in infants at high risk for developing RDS is a safe and effective modality of respiratory support which decreases ventilatory requirements, improves respiratory status, and causes early extubation [25]. Henrik Verder et al in a multicenter RCT found that need of prolonged mechanical ventilation and/or early death within 7 days of age was reduced from 63% (in late treated infants) to 21% (in early treated infants) [16]. In our study, taking reference duration of ≥ 3 days for extra ventilation (or earlier death while being on ventilatory support), we found it to be 45% in late therapy and 31% in early treatment group.

In our study, culture positive sepsis was found in 68% ($n=68$), culture negative sepsis in 9% and 23 babies had no sepsis. Significant difference was found between study groups indicating significantly higher occurrence/pre-existence of culture positive sepsis in subjects receiving late surfactant therapy ($p=0.033$) and similarly difference between early and late groups had been observed by Jayachandra et al [23].

Among complications, hypotension or worsening shock was more frequently encountered in subjects receiving late surfactant therapy ($p=0.029$), whereas no significant difference was noted between study groups for pulmonary hemorrhage ($p=0.58$) and apnea ($p=0.38$). 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 [17,19–21,24], although incidence of pneumothorax was similar with early and late therapy in few studies [14,22].

Conclusion

Respiratory distress syndrome is the most common co-morbidity related to prematurity and CPAP support with early surfactant supplementation is recommended therapy for it. 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 need of mechanical ventilation, early therapy reduced its duration. In our study setup, more than two third subjects had culture proven sepsis showing higher association with late therapy; and among complications, hypotension occurred more frequently after late therapy while pulmonary hemorrhage and apnea had similar occurrence with both early and late therapy.

Limitations of The Study: Poor outcome in this study with overall high mortality despite of surfactant therapy cannot be attributed to only surfactant therapy (type/preparation/single dosing, timing or even delay in surfactant administration) because of existence of multiple additional risk factors like higher proportion of extreme preterm and/or ELBW subjects, more out born with delayed admissions, and high prevalence of sepsis in this study population.

Thus, similar study in multicenter setup including larger population of more premature and extremely LBW subjects but with minimal sepsis or other confounding factors is warranted to strongly support the true benefits of early surfactant therapy in terms of higher survival, less complications and less need of mechanical ventilation.

What this study adds to existing knowledge/practice: This study supports and strengthens the favorable outcome of early and prophylactic surfactant therapy (over delayed rescue treatment strategy) that can be applicable even at resource limited settings.

Contributions by authors: Phuljhele S- conceived and supervised the study and helped in manuscript writing, she will act as second correspondence author. Chukkanakal J- written the protocol, recruited patients and helped in analysis and manuscript writing.

Rathia SK- helped in protocol writing and conceptualization, analyzed data, prepared and finalized the manuscript; he will be the corresponding author and guarantor. The final manuscript had been approved by all authors.

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