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Comparison of Early versus a Late Administration of Surfactant in Newborns with Respiratory Distress Syndrome

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Respiratory Distress Syndrome, Premature newborn, Surfactant Therapy, Neonatal Mortality, Maternal Comorbidities

Abstract

Background: *Respiratory distress syndrome (RDS) remains a leading cause of morbidity and mortality among premature newborns. Along with CPAP support, surfactant replacement therapy plays a critical role in determining outcomes. This study aimed to compare outcomes between early and late surfactant administration among preterm infants (<34 weeks) with RDS.* ***Methods:*** *Sixty preterm neonates were enrolled and divided equally into early and late surfactant groups. Both groups were comparable in terms of gestational age, birth weight, sex distribution, and maternal comorbidities. Maternal risk factors and neonatal complications were analyzed to identify associations with survival outcomes.* ***Results:*** *Early surfactant administration was more frequent among inborn newborns (73.3% vs. 56.7%). Although sepsis, NEC, and PDA occurred in both groups, higher frequencies of sepsis (56.7% vs. 40%) and mortality (66.7% vs. 30%) were observed in the late surfactant group (p=0.009). The need for mechanical ventilation was significantly lower in the early therapy group (33.3% vs. 63.3%, p=0.038). Mortality was strongly associated with neonatal sepsis (p=0.001), NEC (p=0.019), PDA (p=0.009), and need for ventilation (p=0.006). Among maternal factors, gestational diabetes mellitus (GDM, p=0.002), premature rupture of membranes (PROM, p=0.007), chorioamnionitis (p=0.028), and pregnancy-induced hypertension (PIH, p=0.004) were significantly linked to newborn death. Logistic regression identified late surfactant administration (OR=0.165, 95% CI: 0.029–0.948), GDM (OR=0.147, 95% CI: 0.035–0.615), and PROM (OR=0.239, 95% CI: 0.061–0.930) as independent predictors of mortality.* ***Conclusion:*** *Early surfactant therapy significantly reduced mortality and ventilation requirements among premature newborns with RDS, underscoring the importance of timely intervention and optimal perinatal care.*

Introduction:

Globally 2.3 million newborns died in the neonatal period in 2022, amounting to 47% of all child deaths under the age of 5 years.[1] In developing countries, over one-third of under-five deaths are due to newborn mortality, with around 75% within the first week of life. The leading causes of newborn mortality are premature birth, birth complications (perinatal asphyxia/trauma), infections and congenital anomalies.[1] Respiratory difficulty, due to various causes like- respiratory distress syndrome (RDS), congenital pneumonia,

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meconium aspiration syndrome etc., occurs in approximately 0.96% to 12% of live births and is the most common issue newborns face within the first 72 hours, often leading to admission to the neonatal intensive care unit.[2]

Respiratory distress syndrome (RDS) is the most common co-morbidity among premature newborns. More than half of newborns with very low birth weight (VLBW, <1500 grams) exhibit clinical signs of RDS, which is also the leading reason for initiating mechanical ventilation in newborns.[3] The mainstay in the treatment of respiratory distress syndrome (RDS) is respiratory support combined and surfactant therapy. Continuous positive airway pressure (CPAP) and mechanical ventilation (MV) are the most commonly used respiratory support. CPAP helps maintaining functional residual capacity (FRC) by preventing alveolar collapse and pulmonary shunting. It also reduces obstructive apnea and respiratory effort by stabilizing both large and small airways, while protecting against surfactant degradation. However, 40–60% of infants with RDS treated with CPAP alone may fail and require mechanical ventilation. Surfactant replacement therapy has significantly altered the course of RDS, leading to up to a 40% reduction in neonatal mortality and a 30–65% decrease in the risk of pneumothorax.[4,5]

Surfactant is a chemical substance made of phospholipids and proteins that lines the alveoli and reduces surface tension, preventing alveolar collapse. In preterm infants, surfactant deficiency leads to the development of respiratory distress syndrome (RDS). Administering surfactant directly into the trachea has been shown to lower both mortality and morbidity in neonates with RDS. The use of exogenous surfactant in neonates with RDS can improve survival, reduce the need for mechanical ventilation, shorten NICU stays, and lower treatment costs.[5] The first clinical use of exogenous surfactant to treat RDS was reported by Fujiwara and colleagues in 1980. Since then, various artificial surfactants have been commercially developed and adopted as standard therapy for RDS worldwide. Although surfactant administration can lead to complications such as hypotension, shock, apnea, bradycardia, pneumothorax, pulmonary interstitial emphysema (PIE), and pulmonary hemorrhage, it remains the standard of care in premature newborns with RDS. Surfactant therapy is linked to reduced neonatal mortality, lower rates of pneumothorax, and improved survival without bronchopulmonary dysplasia (BPD).[3]

Currently, animal-derived natural surfactants—primarily from bovine or porcine sources—are widely used as the treatment options for RDS. Available under various brand names with differing doses, concentrations, and costs, these surfactants have significantly improved the survival of preterm, low birth weight (LBW), and very low birth weight (VLBW) infants, contributing to reductions in both neonatal and infant mortality.[3]

Randomized controlled trials have demonstrated that early administration of surfactant results in better outcomes for preterm infants compared to delayed treatment. Current evidence suggests that neonates who receive adequate antenatal steroids and early CPAP are less likely to require subsequent mechanical ventilation. Recent trials have further indicated that a substantial number of preterm infants can be effectively managed with CPAP alone, without the need for surfactant. In resource-limited facilities, where nursing support is inadequate and the risk of hospital acquired infection is high, minimizing the need for and duration of mechanical ventilation and CPAP is crucial.

Early administration of surfactant has the potential to prevent CPAP failure, shorten the overall duration of CPAP therapy and can reduce the requirement for mechanical ventilation. At our center, preterm newborns with RDS who do not require intubation during initial resuscitation and present with respiratory distress are started on CPAP. Rescue surfactant is administered if the infant requires ≥50% FiO_2 after the first two hours of life. Surfactant is a costly medicine. Due to their financial constrain, many parents can't afford it and those candidates are to keep on CPAP only. Sometimes parents manage it later on depending on arranging the required expenditure. This study was designed to evaluate the effectiveness of early surfactant administration compared to late use in preterm newborns with RDS managed on CPAP.[4]

Systematic reviews have shown that prophylactic surfactant therapy—whether natural or synthetic—can reduce mortality risk by up to 40% and the risk of pneumothorax by 30–65%. Following the establishment of the safety and efficacy of exogenous surfactant in treating neonatal RDS, further studies explored optimal dosing and timing. Numerous studies have examined various surfactant types, doses, administration methods. Early administration, particularly within the first two

hours of life, has been found to prevent alveolar injury and baro-volutrauma. It also significantly reduces the risk of pneumothorax, pulmonary interstitial emphysema (PIE), chronic lung disease (CLD), and mortality. We therefore aimed to determine whether early administration (within 2 hours after birth) of surfactant would be superior to late surfactant treatment (after 2 hours) in preterm infants with RDS.[6]

Methods:

This was an open-label randomized controlled trial was conducted in a level III neonatal intensive care unit (NICU) over six months period, from 1st January 2025 to 30th June 2025, in Institute of Child and Mother Health (ICMH), Matuail, Dhaka-1362. The department has a 21-beded NICU, with six CPAP machines and two mechanical ventilators, with 3 faculties, 12 postgraduate trainee and 15 nurses. The total 236 patients were included in this study.

All the preterm newborns with d" 34 completed weeks of gestational age were included and those having major congenital malformation were excluded from the study.

Neonates were randomly assigned to either the early or late surfactant group. Randomization was done using computer-generated random numbers. The group allocations were placed in serially numbered, opaque, sealed envelopes, which were opened by principal investigator after obtaining informed parental consent. Due to the nature of the intervention, blinding of surfactant administration timing was not feasible; hence, the treating team was aware of the group assignments.

Eligible neonates presenting with clinical features suggestive of respiratory distress syndrome (RDS) were evaluated using the Silverman scoring system, which assesses parameters such as respiratory rate (>60 breaths/min), chest retractions, and grunting. Following the initial evaluation, airway patency, breathing, and circulation were assessed and stabilized as required. Candidates for surfactant replacement therapy were identified according to standardized clinical guidelines. Neonates who received surfactant within 2 hours of birth were categorized as early surfactant recipients, while those who received it after 2 hours of age were categorized as late surfactant recipients.

Eligible neonates received continuous positive airway pressure (CPAP) using a bubble CPAP generator (Fisher and Paykel Healthcare, Inc.) with nasal mask. The initial CPAP pressure was set at 5 cm H, O. If chest radiograph findings were suggestive of respiratory distress syndrome (RDS)—low lung volumes, reticulo granularity, or air bronchogram—parental consent was obtained for enrolment and randomization following admission to the neonatal intensive care unit (NICU).

Neonates with RDS on CPAP assigned to the early surfactant group were briefly intubated for surfactant administration and extubated back to CPAP. Those in the late surfactant group remained on CPAP and received surfactant if FiO, requirements exceeded 0.50 beyond 2 hours of life.

Endotracheal tube position was confirmed by tube length at the lip, symmetry of breath sounds, and chest wall movement. Natural origin surfactant (bovine - Survanta)—was administered at 100 mg/kg in two to three aliquots. After each aliquot, positive pressure ventilation was provided with a self-inflating neonatal resuscitation (AMBU) bag. Following completion of surfactant administration, neonates maintaining oxygen saturation between 87–93% were extubated back to CPAP.

Adjustments in CPAP were made based on the degree of chest retractions, oxygen saturation (SpO), and lung inflation on chest radiograph, with a maximum pressure limit of 7 cm H, O. The fraction of inspired oxygen (FiO,) was titrated to maintain SpO, between 88% and 92%. CPAP was discontinued when the infant remained stable on a pressure of 4 cm H, O with FiO, < 0.25 for 8–12 hours, after which the infant was transitioned to head box oxygen. Methylxanthines were administered only for the treatment of apneas. None of the infants received nasal intermittent positive pressure ventilation.

Clinical and laboratory parameters were recorded before and after surfactant administration. Any procedural or post-medication complications were managed appropriately. Comparative data were collected on survival or death outcomes (based on timing of surfactant therapy, gestational age, and birth weight), improvement in post-surfactant Silverman score, need for and duration of subsequent ventilation, complications related to surfactant therapy, and the association between culture-positive or culture-negative sepsis and mortality.

The primary outcome was the requirement for mechanical ventilation (MV) while hospitalization. Indications for MV included: CPAP pressure >7 cm H, O and/or FiO, >0.70 required to maintain SpO, >88%; arterial PaCO, >55 mm Hg with pH

<7.20 in association with increasing respiratory distress, as measured by the Silverman score; and recurrent or severe apnea, defined as >4 episodes per hour or the need for bag-and-mask ventilation 1–2 times per hour.

Data were recorded in Microsoft Excel and expressed as percentages or mean ± standard deviation (SD). Categorical variables were compared using the χ^2 test. Statistical significance was defined as $p < 0.05$ for predefined outcome variables. Logistic regression was performed to assess the effect of study group on the primary outcome, adjusting for gender, birth weight, small-for-gestational-age status, antenatal steroid exposure, surfactant brand, and multiple births. Statistical analyses were conducted using SPSS for Windows, version 17 (IBM Corp., NY, USA) and Microsoft Excel 2007 (Microsoft Corp., WA, USA).

Results:

A total 100 newborns were assessed for eligibility, and 40 of them were excluded. Finally, 60 premature enrolled. Of them 30 were allocated in early and rest in late surfactant group.

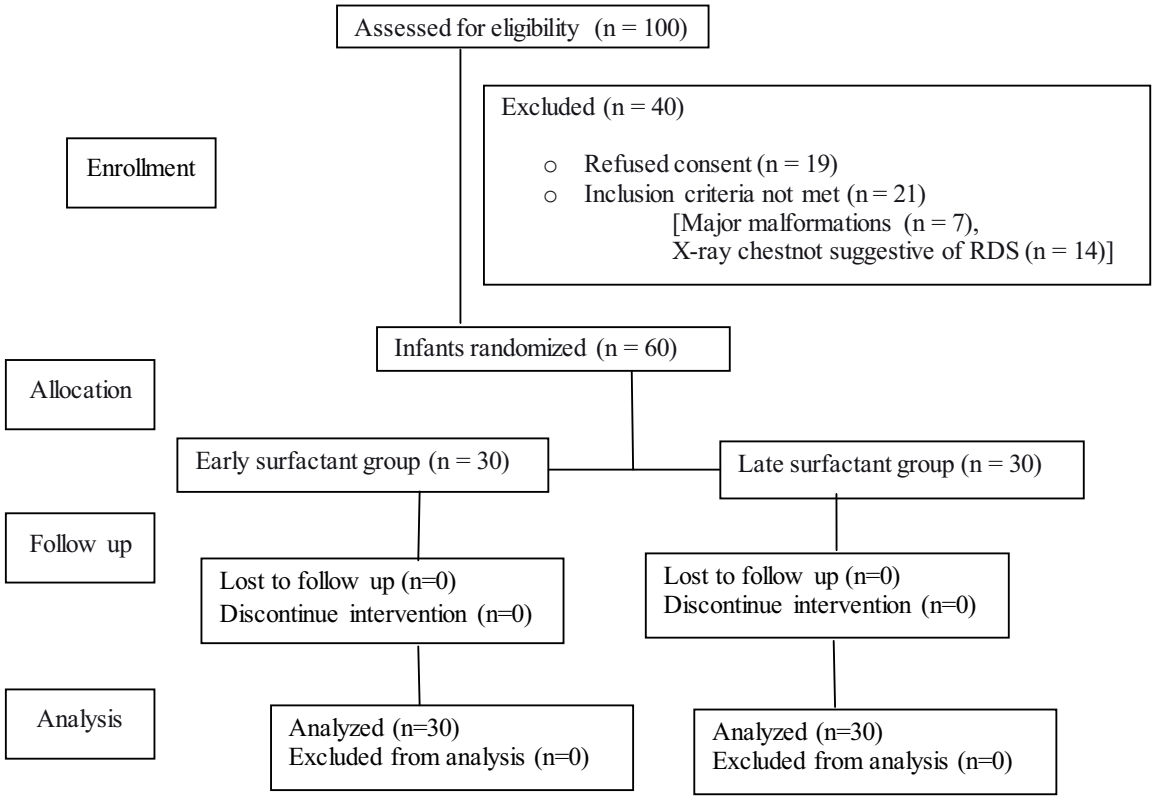

Figure 1: Patients' flow diagram (CONSORT)

Consistent with previous other studies, this study primarily aimed to evaluate the survival benefits of early surfactant administration in a resource-constrained tertiary care public hospital, where multiple mortality risk factors exist in addition to prematurity-associated RDS. Secondarily, a key objective was to compare mortality across birth weight and gestational age subgroups in relation to the timing (early vs. late) of surfactant administration. Additionally, immediate complications, the need for mechanical ventilation, and the presence of sepsis were identified as major confounding factors associated with poor outcomes in our study.

A total of 60 premature newborns of gestational age < 34 weeks with different birth weight with clinical features of RDS had been enrolled, where female was predominant (>50%) in both the groups with higher frequency of early surfactant administration feasible in inborn patients, 73.3% vs. 56.7%.

A total of thirty premature newborns of <34 weeks, having clinical features of RDS, were analyzed in each group. On Chi square test the two study groups were found matched in terms of mode and place of delivery, gestational age, birth weight, gender and clinical features at admission. (Table 1)

Table 1. Baseline characteristics of the newborns in between the groups

Variable	Early Surfactant group(n = 30)	Late Surfactant group(n = 30)	p-value
NVD, n/N (%)	21/30 (70%)	19/30 (63.3%)	0.392
Female, n/N (%)	16/30 (53.3%)	19/30 (63.3%)	0.300
Gestation (weeks):			
<30 weeks, n/N (%)	9/30 (30%)	14/30 (46.7%)	0.144
30-34 weeks, n/N (%)	21/30 (70%)	16/30 (53.3%)	
Birth weight (grams)			0.292
<1000, n/N (%)	9/30 (30%)	16/30 (53.33%)	
1000-1199, n/N (%)	7/30 (23.3%)	6/30 (20%)	
1200-1499, n/N (%)	8/30 (26.7%)	5/30 (16.67%)	
>1500,	6/30 (20%)	3/30 (10%)	
Clinical features: cyanosis along with grunting, severe chest indrawing and tachypnea.	7/30(23.3%)	9/30 (30.0%)	0.771
Inborn n/N (%)	22/30 (73.3%)	17/30 (56.7%)	0.139
Post-natal age at surfactant administered-			
< 2h	30 (100%)	—	
2-6h	00	03 (10%)	
6-24h	00	12 (40%)	
After 24h	00	15 (50%)	

*NVD- normal vaginal delivery. Chi square test suggests the two study groups were matched for gender (i.e. with non- significant p=0.50.

In both the groups, there was female predominance, 53.3% (16/30) and 63.3% (19/30) respectively in early and late surfactant group. Among the newborns, majority were inborn (73.3% and 56.7%) and delivered by NVD (70% & 63.3%). Most of the newborns were from gestational age group of 30-34 weeks (21 and 16 out of 30 in each group). Grunting, severe chest indrawing and tachypnea were predominant clinical features among the newborns, and few newborns had cyanosis in addition (23.3% and 30%). A higher frequency (73.3 vs 56.7%) of early administration of surfactant were observed among newborns who were inborn. (Table 1)

Table 2. Baseline characteristics of the mothers in between the groups

Variable	Early Surfactant group (n = 30)	Late Surfactant group (n = 30)	p-value
Primipara, n/N (%)	20/30 (66.7%)	13/30 (43.3%)	0.119
ACS			0.140
Completed 2 doses	3/30 (10%)	8/30 (10%)	
Completed 1 dose only	5/30 (16.7%)	7/30 (16.7%)	
Not a single dose	22/30 (73.3%)	15/30 (73.3%)	
GDM	8/30 (26.7%)	11/30 (36.7%)	0.580
PROM*	8/30 (26.7%)	14/30 (46.7%)	0.180
Chorioamnionitis	10/30 (33.3%)	10/30 (33.3%)	1.000
PIH**	14/30 (46.7%)	11/30 (36.7%)	0.601

*ACS- Antenatal corticosteroid (12.5 mg of Dexamethasone, 2 doses, I/M- 12 hour apart),
**PIH- Pregnancy induced hypertension

The baseline characteristics of the mothers in between the groups were also matching. (Table 2). Among the mothers, 26.7% and 36.7% of them were suffering from gestational diabetes mellitus (GDM), 26.7% and 46.7% had experienced premature rupture of membrane (PROM), 33.3% had features of chorioamnionitis in each group, 46.7% and 36.7% of mothers were suffering from pregnancy induced hypertension (PIH) in early and late surfactant group respectively. (Table 2)

Among newborns, total 40% and 56.7% babies had features of sepsis, of them culture positive septicemia was documented in 23.3% (7/30) and 43.3% (13/30) in early and late surfactant group respectively and rest had positive laboratory parameters and clinical features only. Newborns in the late surfactant group showed a higher rate of sepsis, though the difference was not significant (p=0.257). (Table 3)

Almost 23% newborns in early and 30% in late surfactant group developed NEC. Almost half of the newborns in each group, 17 and 13 in early and late surfactant group respectively, was had features of PDA (p=0.439). Among all the studied newborns, 10 (6 in early and 4 in late surfactant group) developed pulmonary hemorrhage, counting for 16.7% of all. None of the newborns in our study developed pneumothorax. Out of 60 newborns, 20 (33.3%) required ventilation within 24 hours of receiving surfactant therapy. There was no statistically significant difference between the two groups regarding the need for ventilation following surfactant administration (p=0.170). Specifically, 7 out of 30 newborns (35%) in the early therapy group and 13 out of 30 (65%) in the late therapy group required ventilation. During the hospital stay, 29 newborns (48%) required ventilation. In the early therapy group, 10 out of 30 newborns (33.3%) required ventilation, compared to 19 out of 30 (63.3%) in the late therapy group, (p=0.038). (Table 3)

Table 3. Complications in the Early and Late surfactant group

Variable	Early Surfactant group, n/N (%)	Late Surfactant group, n/N (%)	p-value
Sepsis			0.257
Blood C/S +ve sepsis	05/30 (16.7%)	13/30 (43.3%)	
CF + Lab +ve & not blood C/S +ve	07/30 (23.3%)	04/30 (13.3%)	
No sepsis	18/30 (60%)	13/30 (43.3%)	
NEC	7/30 (23.3%)	9/30 (30%)	0.771
PDA	17/30 (56.7%)	13/30 (43.3%)	0.439
Pulmonary hemorrhage	6/30 (20%)	4/30 (13.3%)	0.731
MV Needed within 24h of surfactant administration	7/30 (23.3%)	13/30 (43.3%)	0.170
MV needed ever during hospitalization	10/30 (33.3%)	19/30 (63.3%)	**0.038**
Death	09/30 (30.0%)	20/30 (66.7%)	**0.009**

*CF- clinical feature **MV- mechanical ventilation

A significant proportion of newborns who developed sepsis (21 out of 29; 72.4%) did not survive, (p=0.001). (Table 5) Significant association was observed in between the occurrence of sepsis and NEC among the studied premature newborns (p = 0.019). (Table IV) Mortality was significantly higher among newborns who developed NEC, with 12 of 16 (75%) not surviving (p=0.019). Of them who had PDA 66.7% had died (p=0.009). 70% of newborn who developed pulmonary hemorrhage had died (p=0.175). Among those who required ventilation, a significantly higher mortality rate was observed (15/20; 75%, p=0.006). Among those who required ventilation, mortality remained significantly high, with 20 of 29 newborns (69%) not surviving (p=0.004).

Table 4 also reveal difference on **mortalityrates** between various birth weight bands (p=0.051) and gestation age subgroups (p=0.062). Despite the lack of statistical significance, extremely immature and low birth weight newborns showed overall poor outcomes, negating the survival advantage of surfactant regardless of when it was administered.

Table 4. *Sepsis and NEC as complications among the studied newborns*

Variable	Sepsis	No sepsis	p-value
NEC	12 (41.4%)	4 (12.9%)	**0.019**
No NEC	17 (58.6%)	27 (87.1%)	

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Of the 60 newborns in the study, 31 survived intact following surfactant therapy, while 29 died due to respiratory distress syndrome (RDS) and/or associated comorbidities. Mortality was significantly higher in the late surfactant therapy group, with 20 of 30 newborns (66.7%) compared to 9 of 30 (30%) in the early therapy group (p=0.009).

No statistically significant differences in survival and death outcomes were observed between the two study groups (based on surfactant timing) for gestational age subgroups (p=0.062) or birth weight categories (p=0.051).

Table 6. Survival outcome in different maternal conditions

Variable	Survival (n/N, %)	Death (n/N, %)	p-value
Parity-			
Primipara	16/33 (48.5%)	17/33 (51.5%)	0.614
Multipara	15/27 (55.6%)	12/27 (44.4%)	
Missed Antenatal corticosteroid (ACS)	18/37 (48.6%)	19/37 (51.4%)	0.603
Mother had GDM	04/19 (21.1%)	15/19 (78.9%)	0.002
Mother had PROM	6/22 (27.3%)	16/22 (72.7%)	0.007
Mother had chorioamnionitis	06/31 (19.4%)	14/29 (48.3%)	0.028
PIH	07/31 (22.6%)	18/29 (62.1%)	0.004

*MV- mechanical ventilation

Among the maternal co-morbidities, gestational diabetes mellitus (GDM, p=0.002), premature rupture of membrane (PROM, p=0.007), chorioamnionitis (p=0.028) and pregnancy induce hypertension (PIH, p=0.004) were individually found as significant risk factor for mortality irrespective of timing of surfactant use. Among them only GDM (p= 0.009, OR = 0.147, 95% CI: 0.035–0.615) and PROM (p=0.039, OR =0.239, 95% CI: 0.061–0.930) were found potential maternal comorbidities determining death after binary logistic regression analysis. (Table 7)

Table 7. Binary logistic regression analysis of potential maternal comorbidities determining death among the premature newborns with RDS

Maternal comorbidities	aOR	95% CI		*p*-value
		Lower	Upper	
Gestational Diabetes Mellitus (GDM)	0.147	0.035	0.615	0.009
Premature Rupture Membrane (PROM)	0.239	0.061	0.930	0.039
Chorioamnionitis	0.419	0.087	2.009	0.277
PIH	0.423	0.094	1.907	0.263

In the logistic regression analysis, GDM (OR = 0.147, 95% CI: 0.035–0.615) and (OR = 0.239, 95% CI: 0.061–0.930) PROM were found significant determinants of newborn death from RDS irrespective of timing of surfactant administration.

Table 5. Survival outcome in different newborn conditions

Variable	Survival (n/N, %)	Death (n/N, %)	P value
Male	14/25 (56%)	11/25 (44%)	0.609
Gestational Age in weeks			0.062
<30 weeks	08/23 (34.8%)	15/23 (35.2%)	
30-34 weeks	23/37 (62.2%)	14/37 (37.8%)	
Birth weight			0.051
< 1000g	10/25 (40%)	15/25 (60%)	
1000-1199g	05/13 (38.5%)	08/13 (61.5%)	
1200-1499g	08/13 (61.5%)	05/13 (38.5%)	
>1500g	08/09 (88.9%)	01/09 (11.11%)	
Sepsis	8/29 (27.6%)	21/29 (72.4%)	0.001
NEC	4/16 (25%)	12/16 (75%)	0.019
Pulmonary Hemorrhage	03/10 (30%)	07/10 (70%)	0.175
PDA	10/30 (33.3%)	20/30 (66.7%)	0.009
MV Needed within 24h of surfactant administration	5/20 (25%)	15/20 (75%)	0.006
MV needed ever during hospitalization	9/29 (31%)	20/29 (69%)	0.004
CPAP with early surfactant	21/30 (70.0%)	09/30 (30.0%)	0.009
CPAP with late surfactant	10/30 (33.3%)	20/30 (67.7%)	

Table 8. Binary logistic regression analysis of potential newborn conditions determining death among the premature newborns with RDS

Newborn conditions	aOR	95% CI		*p*-value
		Lower	Upper	
Sepsis	0.226	0.037	1.395	0.109
NEC	0.411	0.084	2.013	0.272
PDA	0.316	0.042	2.399	0.265
MV Needed within 24h of surfactant administration	0.372	0.072	1.916	0.237
MV needed ever during hospitalization	0.361	0.065	2.002	0.244
CPAP with late surfactant	0.165	0.029	0.948	0.043

In the logistic regression analysis, late administration of exogenous surfactant (after 2 hours of delivery) was found as significant determinants of newborn death from RDS irrespective of timing of surfactant administration (OR = 0.165, 95% CI: 0.029 - 0.948).

Among the co-morbidities of newborn, sepsis (p=0. 0.001), NEC (p=0.019), PDA (p=0.019) and late administration of surfactant (p=0.009) were individually found as significant risk factor for mortality. Among them only late administration of surfactant (p=0.043, OR = 0.165, 95% CI: 0.029 - 0.948) was found potential determinant of death after binary logistic regression analysis. (Table 8)

Discussion:

Respiratory distress syndrome, the most prevalent co-morbidity of prematurity, is effectively managed with surfactant replacement therapy, which has been established as both safe and efficacious since the early 1990s.[3] Moreover, evidence indicates that early administration confers significant advantages over late therapy, including reduced mortality and lower rates of immediate and long-term complications.[7,8]

Significant difference was found between early versus late surfactant in respect to need for further mechanical ventilation (p=0. 0.038). Previous two studies by Jayachandra et al. and Kandraju et al. [4] have revealed higher need of mechanical ventilation after late administration of surfactant in comparison to the early interventions (31.6% vs 16.2%, and, 52.6% vs 28.5% respectively).

In consistent with our study, Swarnkar et al.[10] found that of early 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.

In their meta-analysis, Stevens TP, et al.[11] observed that in newborns with RDS, early surfactant therapy followed by extubation to nCPAP compared with later selective surfactant administration was associated with a lower incidence of MV (RR 0.67, 95% CI 0.57– 0.79) and air leak syndrome (RR 0.52, 95% CI 0.28–0.96). This finding was consistent with this study.

None of the newborns developed pneumothorax or air leak syndrome. Similarly decreased risk of pneumothorax chronic lung disease with less overall complications in early group was observed previous similar studies.[12,13] The cautious titration of CPAP pressures may be the reason for the lower incidence of pneumothorax in our study.

In our study, total 40% and 56.7% babies had features of sepsis, of them culture positive septicemia was documented in 23.3% (7/30) and 43.3% (13/30) in early and late surfactant group respectively and rest had positive laboratory parameters and clinical features only and 51.7% babies (n/N=31/60) had no sepsis. Newborns in the late surfactant group showed a higher rate of sepsis (40% vs. 56.6%), though the difference was not significant (p=0.257). This finding was almost similar to the findings of Kandraju H et al.[4] (24.3% vs. 17.7%), Phuljhele S et al.[3] (56.5% vs. 77.8%), Dhale S et al.[14] (52.5% vs. 52.7%).

Necrotizing enterocolitis was also found in almost one-quarter of newborns in each group (23.3 % and 30 %). A significant co-existence of sepsis and NEC was observed her among the newborns (p=0.019) as also observed by Garg, P.M. et al.[15]

Regarding the primary outcome, patients who received late surfactant therapy experienced significantly higher mortality than those who received early therapy (66.7% vs 30%, p = 0.009). These results align with previous meta-analyses, which have similarly reported enhanced survival with early surfactant administration.[16,17]

Another important observation in our study was significant difference on mortality rates between various birth weight {60% for BW bands <1000gms, while 61.5% for 1000-1199 gms. and 38.5% among the birth weight bands of 1200-1500gm. Death rate was 35.2% and 37.8% in gestation age subgroups of < 30weeks and 30-34 weeks bands 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. These findings go similar with Phuljhele S, et al.[3]

Among the maternal co-morbidities, gestational diabetes mellitus (GDM, p=0.002), premature rupture of membrane (PROM, p=0.007), chorioamnionitis (p=0.028) and pregnancy induce

hypertension (PIH, p=0.004) were individually found as significant risk factor for mortality irrespective of timing of surfactant use. Among them only GDM (p= 0.009,OR = 0.147, 95% CI: 0.035–0.615) and PROM (p=0.039, OR = 0.239, 95% CI: 0.061–0.930) were found potential maternal comorbidities determining death after binary logistic regression analysis. This finding was similar with previous similar findings.[18,19]

In this study, several maternal comorbidities-including gestational diabetes mellitus (GDM), premature rupture of membranes (PROM), chorioamnionitis, and pregnancy-induced hypertension (PIH)—were initially found associated with neonatal mortality, irrespective of the timing of surfactant administration. However, multivariate logistic regression identified only GDM and PROM as independent predictors of mortality.

These results are consistent with previous studies showing that maternal GDM increases the risk of adverse neonatal outcomes, including respiratory distress and mortality.[20,21] and that PROM is associated with higher risk of early neonatal infection and mortality.[22,23] Clinically, these findings underscore the importance of careful monitoring and management of pregnancies complicated by GDM and PROM.

Among neonatal comorbidities, sepsis (p = 0.001), necrotizing enterocolitis (NEC, p = 0.019), patent ductus arteriosus (PDA, p = 0.019), and late surfactant administration (p = 0.009) were each identified as significant risk factors for mortality. However, on binary logistic regression analysis, only late surfactant administration (p = 0.043; OR = 0.165; 95% CI: 0.029–0.948) remained an independent determinant of death.

Similar findings have been documented in multiple recent studies investigating neonatal comorbidities in relation to mortality outcomes. Goh et al.[24] identified late-onset sepsis as a major predictor of mortality among very low birth weight (VLBW) infants, while Kolesnichenko et al.[25] and Milton et al.[26] likewise highlighted neonatal sepsis as a key determinant of early neonatal deaths across diverse clinical contexts.

Necrotizing enterocolitis (NEC) has consistently been associated with increased neonatal mortality. Lopes et al.[27] and Alene T et al.[28] identified NEC as a leading cause of death among very low birth weight (VLBW) infants, often occurring in conjunction with sepsis and hemodynamic instability. Patent ductus arteriosus (PDA) similarly remains an important comorbidity linked to mortality and prolonged ventilatory dependence in preterm neonates with respiratory distress. Regarding surfactant therapy, studies by van Kaam et al.29, Chavan et al.[30], and Kavurt et al.[31] have demonstrated that early surfactant administration markedly reduces the incidence of complications such as PDA, NEC, and death compared with delayed administration.

Similarly, Hascoet et al.[32] and Kariniotaki et al.[33] emphasized that timely respiratory management-including appropriate surfactant administration and stringent infection control-is crucial for improving survival among preterm and late-preterm infants. Collectively, these findings corroborate the present analysis, highlighting neonatal sepsis, NEC, PDA, and delayed surfactant administration as pivotal determinants of mortality and reinforcing the importance of early intervention and vigilant perinatal care for an optimized neonatal outcome.

Conclusion:

In conclusion, this study demonstrates that early administration of exogenous surfactant within two hours of birth significantly improves survival among preterm neonates with respiratory distress syndrome (RDS). Late surfactant therapy was independently associated with increased mortality, even after adjustment for confounding factors.

Limitations:

This study has several limitations. The relatively small sample size and single-center design may limit the generalizability of the findings. Although baseline characteristics were comparable between groups, unmeasured confounders—such as timing of referral for out born neonates, and variations in clinical management—may have influenced outcomes. Neonatal complications including sepsis, NEC, and PDA were diagnosed based on clinical and limited laboratory criteria, which may have led to under- or overestimation of their incidence. Additionally, only a single-dose surfactant regimen was used, and long-term respiratory or neurodevelopmental outcomes were not assessed.

These factors should be considered when interpreting the results and planning future studies.

Data Availability:
The datasets analysed during the current study are not publicly available due to the continuation of analyses but are available from the corresponding author on reasonable request.

Conflict of Interest:
The authors stated that there was no conflict of interest in this study.

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Ethical consideration:
The study was approved by the Ethical Review Committee of Institute of Child & Mother Health, Dhaka, Bangladesh. Informed consent was obtained from each participant or caregivers of the patients.

Contributions by authors: Dr. Abdullahel Amaan had conceptualized the study idea, gone through the literature reviews and constructed the study framework. Dr. Abdullahel Amaan, Dr. Khainoor Zahan and Dr. Mohammad Ala Uddin verified the study procedure and analytical methods and actively participated in communicating with the caregivers. Professor Dr. Md. Mozibur Rahman and Professor Dr. Md. Abdul Mannan encouraged and supervised the study. The final manuscript had been approved by all authors.

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