Outcomes Comparison of Early versus Late Surfactant Replacement Therapy in Neonates with Respiratory Distress Syndrome

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ABSTRACT

Objective: To compare durations of invasive mechanical ventilator (IMV), other types of ventilator support and neonatal outcomes between neonates who received early versus late surfactant replacement therapy (E-SRT vs. L-SRT).

Materials and Methods: This retrospective study included neonates with gestational age (GA) less than 35 weeks or birth weight (BW) less than 2,000 grams, born between January 1, 2017 to December 31, 2021. Neonates who received SRT before 2 hours of life were defined as E-SRT and neonates who received SRT later were defined as L-SRT. Durations of IMV, other types of ventilator support, neonatal outcomes and length of stays were documented.

Results: Eighty-three neonates had received SRT with 52 (62.7%) had E-SRT and 31 (37.3%) had L-SRT. Neonates in E-SRT group had significantly lower GA and BW than neonates in L-SRT group (median GA 27 vs. 30 weeks; $p = 0.002$ and median BW 885 vs. 1330 grams; $p = 0.003$) and had longer duration of IMV but not significant (median 19.0 vs. 10.5 days; $p = 0.219$). There were no significant differences in durations of other types of ventilator support. After adjusted for sex, GA and BW, there were no significant differences in neonatal outcomes between neonates in each group. Ventilator-associated pneumonia (VAP) and septicemia were independent factors associated with prolonged IMV, ventilator supports and length of stays.

Conclusion: Timing of SRT was not associated with duration of IMV. VAP and septicemia were important factors prolonging ventilator durations and length of stays and should be prevented.

Keywords: surfactant replacement therapy, respiratory distress syndrome, timing of surfactant, neonatal outcomes
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INTRODUCTION

Respiratory distress syndrome (RDS) is an important disease affecting preterm neonates worldwide leading to acute neonatal respiratory failure and deaths.[1] Since the introduction of maternal antenatal corticosteroid injection and surfactant replacement therapy (SRT) for neonates, the mortality and morbidity rates of neonates with RDS have decreased dramatically with 30-40% reduction in neonatal mortality and 35-60% reduction in pneumothorax and air leak syndrome.[2] Improvements in non-invasive ventilation (NIV) support for neonates, for example nasal continuous positive airway pressure (NCPAP) or heated humidified high-flow nasal cannula (HHHFNC), has further decreased the need for intubation, invasive mechanical ventilation (IMV) support and SRT among neonates with mild to moderate RDS.[3]

However, NIV support may have been failed in some neonates with severe RDS and SRT is still necessary. For

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these neonates, studies showed that early SRT (E-SRT) given within 2 hours of life could reduce the duration of IMV and NIV[4,5] but with increased risks of air leak syndrome.[6] SRT could be given by several techniques such as endotracheal tube with continuous IMV technique (ETT-IMV), intubation-surfactant-extubation technique (INSURE)[7], or less-invasive surfactant administration technique (LISA).[8] However, due to the high cost of surfactant, E-SRT was not given to every neonate and neonates with moderate RDS could deteriorate and eventually needed SRT later beyond 2 hours of life. Late SRT (L-SRT) may lead to prolonged IMV and respiratory complications such as bronchopulmonary dysplasia (BPD) and ventilator-associated pneumonia (VAP).[9]

The primary objective of the study was to compare duration of IMV between neonates with RDS receiving E-SRT and L-SRT. Other objectives included duration of NIV and oxygen therapy, treatment complications, morbidities and mortality among neonates.

MATERIALS AND METHODS

In this retrospective study, we reviewed medical documents of neonates with gestational age (GA) less than 35 weeks or birth weight (BW) less than 2,000 grams, born between January 1, 2017 and December 31, 2021, at Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, Thailand, who were diagnosed with RDS and had received at least one dose of SRT. Neonates with missing or incomplete medical record would be excluded from the study.

Neonates were grouped into E-SRT group, defined as receiving SRT before 2 hours of life, and L-SRT group, defined as receiving SRT after 2 hours of life. Types of surfactants that neonates received were poractant alfa (Curosurf®, Chiesi Farmaceutici, Italy) or beractant (Survanta®, AbbVie, USA). Criteria for SRT included 1) neonates who were at risk for developing RDS (GA less than 35 weeks), 2) neonates with clinical and radiographic evidences of RDS, and 3) neonates who required FiO_2 more than 40% regardless of types of ventilator support.[10,11] Dosage of SRT ranged from 100-200 mg/kg of phospholipid depended on surfactant products with recommended doses were 200 mg/kg for poractant alfa and 100 mg/kg for beractant. After first dose of SRT, if the neonates clinically deteriorated with FiO_2 requirement reached 40% then additional doses of SRT could be given with time interval no less than 12 hours from each dose and no more than 3 doses in total. Dosage of subsequent SRT were 100 mg/kg of phospholipid for both poractant alfa and beractant.

SRT could be given alone or mixed with budesonide with the aim to prevent BPD. Currently, there is no standard guideline recommending the usage of budesonide, therefore, the decision to administered budesonide was at neonatologists' discretion based on risk for developing BPD such as neonates with GA less than 28 weeks and did not receive a completed course of antenatal corticosteroid. Neonates with risk for infection such as neonates with history of maternal chorioamnionitis or sepsis would not be given budesonide.[12,13]

Collected data included demographic data, maternal characteristics, types, doses and numbers of surfactants used for SRT, methods of SRT, duration of IMV and NIV, duration of oxygen therapy, complications during hospitalization such as air leak syndrome, BPD defined as neonates that needed oxygen supplement at 36 weeks postmenstrual age (PMA) according to National Institute of Child Health and Human Development (NICHD) 2018 criteria[14], VAP, retinopathy of prematurity (ROP), septicemia, necrotizing enterocolitis (NEC), hemodynamically significant patent ductus arteriosus (hsPDA), mortality rate and length of hospital stays.

Statistical analyses were performed using IBM SPSS Statistics, version 26.0 (IBM Corp., Armonk, NY, USA). Percent, ratio, mean ± standard deviation (SD), mean difference, median with interquartile range (IQR) and difference of medians were used to present descriptive data. Correlation analyses were performed by using chi-square test, Fisher's exact test, Student t-test, or Mann-Whitney U-test and presented in odd ratios. A p-value of less than 0.05 was considered to be statistically significant. Multivariate regression analysis was done to minimize confounding factors and identify possible risks associated with outcomes. This study was approved by the Ethics Committee for Human Research at Khon Kaen University (HE651192).

RESULTS

There were 434 neonates with GA less than 35 weeks or BW less than 2,000 grams born during the study period, of which 83 (19.1%) had received SRT. Among neonates that received SRT, 52 (62.7%) had E-SRT and 31 (37.3%) had L-SRT. Neonates who received E-SRT had significantly lower BW [median 885 (IQR 795,1195) vs. 1330 (IQR 895,1580) grams, difference of medians 280 (95%CI 80-485) grams; $p = 0.003$] and GA [median 27 (IQR 25,29) vs. 30 (IQR 27,31) weeks, difference of medians 2 (95%CI 1-3) weeks; $p = 0.002$] than neonates who received L-SRT. More mothers in E-SRT group had multiple medical conditions than mothers in L-SRT group though not statistically significant (30.8% vs. 22.6%; $p = 0.116$). Multiple gestation was the

most common medical condition among mothers in E-SRT group while hypertension was the most common condition among mothers in L-SRT group. Also, twin-twin transfusion syndrome and acardiac twins were found only among mothers in E-SRT group. Mothers in both groups similarly received antenatal corticosteroid and medications. Mothers in E-SRT group tended to have more complications of pregnancy than mothers in L-SRT group but not statistically significant (90.4% vs. 74.2%; $p = 0.093$). Neonatal and maternal characteristics were shown in Table 1.

TABLE 1. Neonatal and maternal characteristics.

	Early SRT N = 52 (%)	Late SRT N = 31 (%)	Difference of medians (95%CI)	*P*-value
Neonatal characteristics				
Sex (Male)	33 (63.4)	19 (61.3)	-	0.843
Body type			-	0.736
SGA	3 (5.8)	2 (6.4)	-	
AGA	48 (92.3)	29 (93.6)	-	
LGA	1 (1.9)	0 (0.0)	-	
Admission status			-	0.054
In-born	49 (94.2)	25 (80.6)	-	
Out-born	3 (5.8)	6 (19.4)	-	
Birth weight (grams)†	885 (795, 1195)	1330 (895,1580)	280 (80-485)	0.003*
Gestational age (weeks)†	27 (25,29)	30 (27,31)	2 (1-3)	0.002*
Maternal characteristics				
Serology status				0.357
Normal	50 (96.1)	28 (90.3)	-	
Abnormal	2 (3.9)	3 (9.7)	-	
HBsAg	2 (3.9)	2 (6.5)	-	
VDRL	0 (0.0)	1 (3.2)	-	
Medical condition§				0.135
Single condition	**17 (32.7)**	**17 (54.8)**		
Multiple conditions	**16 (30.8)**	**7 (22.6)**		
Multiple gestation	13	5	-	
Hypertension	11	12	-	
Elderly primigravida	8	4	-	
Diabetes	4	2	-	
Twin-twin transfusion	4	0	-	
No antenatal care	4	2	-	
Congestive heart failure	4	0	-	
Urinary tract infection	3	2	-	
Acardiac twins	2	0	-	
End-stage renal disease	2	0	-	
Drug abuse	0	2	-	
Thyroid	1	0	-	

TABLE 1. Neonatal and maternal characteristics. (Continued)

	Early SRT N = 52 (%)	Late SRT N = 31 (%)	Difference of medians (95%CI)	*P*-value
Amniotic fluid status				0.847
Normal	41 (78.8)	26 (83.9)	-	
Oligohydramnios	7 (13.5)	3 (9.7)	-	
Polyhydramnios	4 (7.7)	2 (6.4)	-	
Route of delivery				0.853
Vaginal	18 (34.6)	12 (38.7)	-	
Elective caesarean	1 (1.9)	1 (3.2)	-	
Emergency caesarean	33 (63.5)	18 (58.1)	-	
Antenatal corticosteroid				0.823
None	11 (21.1)	7 (22.6)	-	
Partial	14 (27.0)	10 (32.2)	-	
Complete	27 (51.9)	14 (45.2)	-	
Other medication§				0.765
Yes	**37 (71.1)**	**23 (74.2)**	-	
- Antibiotics	23	11	-	
- Magnesium	18	14	-	
- Antihypertensive	6	9	-	
- Tocolytics	9	2	-	
- Insulin	1	0	-	
No	**15 (28.9)**	**8 (25.8)**	-	
Complication of pregnancy§				0.093
Single complication	**13 (25.0)**	**9 (29.0)**	-	
Multiple complications	**34 (65.4)**	**14 (45.2)**	-	
Preterm labor	35	15	-	
Birth asphyxia	32	7	-	
PROM	11	8	-	
Fetal distress	11	4	-	
Placenta previa	6	2	-	
Hydrops fetalis	5	0	-	
Chorioamnionitis	3	2	-	
Birth before arrival	2	3	-	
Abruptio placenta	1	2	-	

Abbreviations: SRT = surfactant replacement therapy, SGA = small for gestational age, AGA = appropriate for gestational age, LGA = large for gestational age, † = median and interquartile range, * = statistically significant, HBsAg = hepatitis B surface antigen, VDRL = venereal disease research laboratory, § = could have more than one conditions, PROM = premature rupture of membrane

Surfactant and respiratory support characteristics

Neonates in E-SRT group were intubated more than neonates in L-SRT group (92.3% vs. 70.9%; $p = 0.010$), and were mostly intubated immediately at labor room while neonates in L-SRT group were mostly intubated later at neonatal intensive care unit (NICU). Neonates in E-SRT group were supported by IMV more than L-SRT group (86.5% vs. 29.0%; $p < 0.001$) and the most frequently used ventilator mode was conventional mode.

The most common surfactant used in each group was poractant alfa followed by poractant alfa mixed with budesonide. Neonates in E-SRT group received more of poractant alfa mixed with budesonide than neonates in L-SRT group although not significant (25.0% vs. 6.4%; $p = 0.099$). Dosage of surfactant used for SRT was similar between each group (158 ± 31 vs. 152 ± 24 mg/kg; $p = 0.976$). The median of timing of SRT in E-SRT and L-SRT group were 1.4 and 5.0 hours, respectively ($p < 0.001$).

The most common technique for SRT was ETT-IMV technique in both groups but neonates in E-SRT group received more SRT via ETT-IMV technique than neonates in L-SRT group (90.4% vs. 51.6%; $p < 0.001$). Also, more neonates in E-SRT group required multiple doses of SRT than L-SRT group (23.1% vs. 6.5%; $p = 0.044$). Surfactant types, SRT techniques and ventilator characteristics were shown in Table 2.

Duration of ventilator supports

Among 83 neonates, 70 neonates were intubated using IMV support with 48 in E-SRT group and 22 in L-SRT group. Overall median of IMV duration was 14.5 (IQR 3.0,32.0) days. Duration of IMV in E-SRT group was longer than L-SRT group but not statistically significant [median 19.0 (IQR 3.0,35.0) days vs. 10.5 (IQR 2.0,28.0) days; difference of medians 3.0 days (95%CI -1.0 to 14.0); $p = 0.219$]. At the age of 60 days, neonates in L-SRT group had significantly higher IMV-free days [median 49.5 (IQR 32.0-58.0) days] than neonates in E-SRT group [median 25.0 (IQR 0.0-42.5) days; $p < 0.001$].

There were 72 neonates receiving NIV support with 41 in E-SRT group and 31 in L-SRT group. Eleven neonates died during IMV and had never received NIV support. Among neonates who received NIV, duration of NIV support was longer in E-SRT group than L-SRT group though not statistically significant [median 42.5 (IQR 26.5,54.0) days vs. 31.0 (IQR 13.0,51.0) days; $p = 0.239$]. However, neonates in L-SRT group had significantly higher NIV-free days at the age of 60 days than neonates in E-SRT group [median 20.0 (IQR 0.0,41.0) days vs. 0.0 (IQR 0.0,22.0) days; $p = 0.034$].

Duration of oxygen usage had a similar trend with IMV and NIV duration, with neonates in L-SRT had higher oxygen free days at the age of 60 days than E-SRT group [median 16.0 (IQR 0.0,36.0) days vs. 0.0 (IQR 0.0,23.0) days; $p = 0.041$].

There were no significant differences in oxygen usage at 28 days, oxygen usage at 36 weeks PMA and home oxygen usage between neonates of each group. Durations of ventilator supports and oxygen supplements were shown in Table 3.

Other outcomes

There were 13 neonates who died before discharge, all of which were in E-SRT group. Neonates in E-SRT group tended to have higher rates of IVH, air leak syndrome, hsPDA, septicemia, VAP, and NEC than neonates in L-SRT group. However, after adjusted for sex, GA and BW, none of the aforementioned outcomes was significantly different.

Among 70 neonates who survived until the timing of diagnosis, ROP and BPD were higher among neonates in E-SRT group than L-SRT group but after adjustment for sex, GA and BW, the difference became insignificant. BPD severity did not differ significantly among neonates in each group, however, rate of stage 3 ROP was higher among neonates in E-SRT group ($p = 0.015$). Also, 10 neonates (25.6%) in E-SRT group required treatment for ROP while none of neonates in L-SRT group needed treatment ($p = 0.004$).

Length of hospital stays between neonates in E-SRT group (mean 70 ± 44 days) and L-SRT group (mean 72 ± 35 days) was similar between both groups (mean difference 1.7 days, 95%CI (-16.8) to 20.3 days; $p = 0.853$). Other outcomes of neonates were shown in Table 4.

Characteristics of non-surviving neonates

Among 52 neonates in E-SRT group, 13 neonates had died; 12 neonates died within 28 days of life (neonatal death) and 1 died after 28 days (post-neonatal death). Of these 13 neonates, 11 were intubated until death while 2 neonates were extubated but died afterward. There were no significant differences in sex, body type, admission status, BW, GA and doses of SRT between neonates who survived and died. Duration of IMV among neonates who died was significantly shorter than neonates who survived [median 4 (IQR 2,14) days vs. 24 (IQR 6,37) days, difference of medians 16 (95%CI 2-26) days; $p = 0.015$]. Similarly, duration of oxygen supplement was

TABLE 2. Surfactant, SRT techniques and ventilator characteristics.

	Early SRT N = 52 (%)				Late SRT N = 31 (%)				*P*-value
Intubation									0.010*
Intubated	48 (92.3)				22 (70.9)				
Never intubated	4 (7.7)				9 (29.1)				
Timing of intubation									<0.001*
Never intubated	4 (7.7)				9 (29.1)				
Immediately at LR	45 (86.5)				8 (25.8)				
Later at NICU	3 (5.8)				14 (45.1)				
Age of Intubation (hours)†	0 (0,0)				4.75 (0,13)				<0.001*
Ventilation mode before SRT									<0.001*
NIV	7 (13.5)				22 (70.9)				
Conventional	30 (57.7)				9 (29.1)				
HFOV	15 (28.8)				0 (0.0)				
Surfactant type	**P**	**P+Bd**	**B**	**B+Bd**	**P**	**P+Bd**	**B**	**B+Bd**	
First dose	37 (71.1)	13 (25.0)	2 (3.9)	0 (0.0)	28 (90.3)	2 (6.4)	1 (3.2)	0 (0.0)	0.099
Second dose	11 (21.1)	0 (0.0)	0 (0.0)	1 (1.9)	2 (6.4)	0 (0.0)	0 (0.0)	0 (0.0)	0.141
Third dose	2 (3.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	N/A
Surfactant dosage (mg/kg)‡									
First dose	158 ± 31				152 ± 24				0.976
Second dose	118 ± 26				131 ± 16				0.542
Third dose	100 ± 0				N/A				N/A
Doses of SRT									0.044*
Single	40 (76.9)				29 (93.5)				
Multiple	12 (23.1)				2 (6.5)				
Timing of first dose SRT (hours)†	1.4 (1,1.8)				5.0 (2.9, 13.5)				<0.001*
SRT technique	**ETT-IMV**	**INSURE**	**LISA**		**ETT-IMV**	**INSURE**	**LISA**		
First dose	47 (90.4)	3 (5.7)	2 (4.2)		16 (51.6)	7 (22.6)	8 (25.8)		<0.001*
Second dose	12 (100.0)	0 (0)	0 (0)		2 (100.0)	0 (0)	0 (0)		N/A
Third dose	2 (100.0)	0 (0)	0 (0)		0 (0)	0 (0)	0 (0)		N/A

Abbreviations: SRT = surfactant replacement therapy, * = statistically significant, P = poractant alfa, P+Bd = poractant alfa and budesonide, B = beractant, B+Bd = beractant and budesonide, ETT-IMV = endotracheal tube with invasive mechanical ventilation technique, INSURE = intubation-surfactant-extubation technique, LISA = less-invasive surfactant administration technique, † = median and interquartile range, ‡ = mean ± standard deviation, SRT = surfactant replacement therapy, NIV = non-invasive ventilation, HFOV = high-frequency oscillatory ventilation

TABLE 3. Durations of ventilator support and oxygen supplements.

Primary outcomes	**Total N = 70**	**Early SRT N = 48**	**Late SRT N = 22**	**Difference of medians (95% CI)**	***P*-value**
Duration of IMV (days)†	14.5 (3.0,32.0)	19.0 (3.0,35.0)	10.5 (2.0,28.0)	3.0 (-1.0 to 14.0)	0.219
IMV-free days at 60 days (days)†	32.0 (14.0,54.0)	25.0 (0.0,42.5)	49.5 (32.0,58.0)	-21.0 (-30.0 to -8.0)	<0.001*
Secondary outcomes	**Total N = 72**	**Early SRT N = 41**	**Late SRT N = 31**	**Difference of medians (95% CI)**	***P*-value**
Duration of NIV (days)†	37.0 (22.0,53.5)	42.5 (26.5,54.0)	31.0 (13.0,51.0)	7.0 (-5.0 to 19.0)	0.239
NIV-free days at 60 days (days)†	3.0 (0.0,29.5)	0.0 (0.0,22.0)	20.0 (0.0,41.0)	-1.5 (-20.0 to 0.0)	0.034*
	Total N = 83	**Early SRT N = 52**	**Late SRT N = 31**	**Difference of medians (95% CI)**	***P*-value**
Duration of oxygen (days)†	44.0 (12.5,79.5)	44.0 (6.0,82.5)	44.0 (24.0,71.0)	-3.0 (-20.0 to 15.0)	0.655
Oxygen free days at 60 days (days)†	0.0 (0.0,28.5)	0.0 (0.0,23.0)	16.0 (0.0,36.0)	-1.0 (-16.0 to 0.0)	0.041*
	Total N = 71 (%)	**Early SRT N = 40 (%)**	**Late SRT N = 31 (%)**	**Adjusted OR (95%CI)**	***P*-value**
Neonates using oxygen at 28 days (%)†,‡	53 (74.6)	31 (77.5)	22 (70.9)	1.41 (0.48-4.11)	0.586
Neonates using oxygen at 36 weeks (%)†,‡	43 (60.6)	27 (67.5)	16 (51.6)	1.95 (0.74-5.13)	0.223
Neonates required home oxygen (%)†,‡	10 (14.1)	6 (15.0)	4 (12.9)	1.19 (0.31-4.65)	0.541

Abbreviations: 95%CI = 95% confidence interval, † = median and interquartile range, * = statistically significant, OR = odd ratio, ‡ = only surviving to discharge neonates

also shorter among neonates who died [median 4 (IQR 2,14) days vs. 57 (IQR 28,85) days, difference of medians 49 (95%CI 21-70) days; $p < 0.001$]. However, duration of NIV was not statistically different. Common causes of death were lung hypoplasia, septicemia and severe IVH. Details about non-surviving neonates were shown in Table 5.

Factors associated with duration of ventilator support and length of stays

Multivariate regression analysis found that factors independently associated with IMV duration were VAP, and septicemia. Neonates who had VAP would have longer duration of IMV than neonates without VAP with mean increase of 19.8 days (95%CI 11.3-28.3 days; $p < 0.001$). Similarly, neonates with septicemia would have longer IMV duration with a mean increase of 13.4 days (95%CI 4.4-22.4 days; $p = 0.004$).

Factors associated with increased duration of NIV were number of SRT dose, and hsPDA. Duration of NIV increased by 19.9 days (95%CI 2.6-37.3 days; $p = 0.025$) per each SRT dose received while having hsPDA increased NIV duration by 13.1 days (95%CI 1.7-24.5 days; $p = 0.025$). In contrary, higher BW or GA, and having completed course of antenatal steroid was associated with decreased duration of NIV. Per each 100 grams increased in BW

TABLE 4. Other outcomes.

Outcomes	Early SRT N = 52 (%)	Late SRT N = 31 (%)	OR (95%CI)	*P*-value	Adjusted OR (95%CI)	*P*-value
Death	13 (25.0)	0 (0.0)	N/A	0.002*	N/A	N/A
Intraventricular hemorrhage	42 (80.7)	24 (77.4)	1.23 (0.41-3.64)	0.715	1.32 (0.36-4.77)	0.674
Grade 1	29 (55.8)	18 (58.1)				
Grade 2	4 (7.7)	3 (9.7)	N/A	0.724	N/A	0.575
Grade 3	3 (5.8)	2 (6.4)				
Grade 4	6 (11.4)	1 (3.2)				
Air leak syndrome	15 (28.8)	7 (22.6)	1.39 (0.49-3.91)	0.532	1.07 (0.34-3.33)	0.908
Hemodynamically significant PDA	26 (50.0)	7 (22.6)	3.43 (1.26-9.34)	0.016*	2.15 (0.72-6.46)	0.173
Septicemia	15 (28.8)	2 (6.4)	5.88 (1.24-27.79)	0.025*	3.08 (0.58-16.33)	0.185
Ventilator-associated pneumonia	30 (57.7)	7 (22.6)	4.67 (1.71-12.78)	0.003*	2.93 (0.97-8.87)	0.058
Necrotizing enterocolitis	10 (19.2)	5 (16.1)	1.24 (0.38-4.03)	0.723	1.33 (0.35-5.03)	0.677
Stage 1	5 (9.6)	5 (16.1)				
Stage 2	3 (5.8)	0 (0.0)	N/A	0.147	N/A	0.274
Stage 3	2 (3.8)	0 (0.0)				
Length of hospital stays (days)‡	70.4 ± 44.5	72.2 ± 34.7	1.7§ (-16.8 to 20.3)	0.853	N/A	N/A
	Early SRT N = 39 (%)	**Late SRT N = 31 (%)**	**OR (95%CI)**	***p*-value**	**Adjusted OR (95%CI)**	***p*-value**
Bronchopulmonary dysplasia†	26 (66.7)	16 (51.7)	1.88 (0.71-4.95)	0.228	1.09 (0.36-3.33)	0.687
Mild	0 (0.0)	3 (9.7)	N/A	0.082	N/A	N/A
Moderate	14 (35.9)	7 (22.6)	1.92 (0.66-5.58)	0.297	1.29 (0.30-5.46)	0.370
Severe	12 (30.8)	6 (19.4)	1.85 (0.60-5.68)	0.281	0.34 (0.05-2.13)	0.309
Retinopathy of prematurity†	20 (51.3)	5 (6.4)	5.46 (1.74-17.24)	0.003*	3.40 (0.91-12.66)	0.068
Stage 1	3 (7.7)	0 (0.0)	N/A	0.249	N/A	N/A
Stage 2	11 (28.2)	5 (16.1)	1.79 (0.54-5.95)	0.391	1.01 (0.26-3.92)	0.985
Stage 3	7 (17.9)	0 (0.0)	N/A	0.015*	N/A	N/A
Neonates received ROP treatment†	10 (25.6)	0 (0.0)	N/A	0.004*	N/A	N/A

Abbreviations: SRT = surfactant replacement therapy, OR = odd ratio, 95%CI = 95% confidence interval, * = statistically significant, ROP = retinopathy of prematurity, ‡ = mean ± SD, § = mean difference, † = Excluded neonates who had died before the timing of diagnosis

TABLE 5. Characteristics of non-surviving neonates.

	Alive N = 39 (%)	Dead N = 13 (%)	Difference of medians (95% CI)	*p*-value
Sex: Male	23 (58.9)	10 (76.9)	-	0.244
Body type				0.801
SGA	2 (5.1)	1 (7.7)	-	
AGA	36 (92.3)	12 (92.3)	-	
LGA	1 (2.6)	0 (0.0)	-	
Admission status				0.303
In-born	36 (92.3)	13 (100.0)	-	
Out-born	3 (7.7)	0 (0.0)	-	
Birth weight (grams)†	890 (820,1205)	830 (690,1082)	90 (-151 to 255)	0.369
Gestational age (weeks)†	27 (25,28)	26 (24,29)	1 (-1 to 2)	0.332
Doses of SRT				0.128
Single	32 (82.1)	8 (61.5)	-	
Multiple	7 (17.9)	5 (38.5)	-	
Duration of IMV (days)†	24 (6,37)	4 (2,14)	16 (2-26)	0.015*
Duration of NIV (days)†	40 (26,54)	28 (11,46)	11 (-29 to 47)	0.512
Duration of Oxygen (days)†	57 (28,85)	4 (2,14)	49 (21-70)	<0.001*
Timing of death				N/A
Early neonatal (≤ 7 d)	-	7 (53.8)	-	
Late neonatal (8-28 d)	-	5 (38.5)	-	
Post neonatal (> 28 d)	-	1 (7.7)	-	
Cause of death				N/A
Lung hypoplasia	-	4	-	
Septicemia	-	3	-	
Severe IVH	-	3	-	
Hydrops fetalis	-	1	-	
HIE	-	1	-	
Pulmonary hemorrhage	-	1	-	

Abbreviations: † = median and interquartile range, * = statistically significant

could reduce NIV duration by 3.2 days (95%CI 1.6-4.8 days; $p < 0.001$). Similarly, each week increased in GA was associated with a 4.1-day (95%CI 1.4-6.6 days; $p = 0.003$) reduction in NIV duration. Having completed antenatal corticosteroid could reduce NIV duration by 6.9 days (95%CI 0.5-13.4 days; $p = 0.035$).

Longer length of stays was associated with number of SRT dose, VAP, septicemia and hsPDA while increased in GA and BW was associated with shorter length of stays. With each week increased in GA associated with 5.4 days (95%CI 2.7-8.0 days; $p < 0.001$) reduction in length of stays. On the contrary, having septicemia, multiple doses of SRT, VAP, or hsPDA would prolong duration of hospitalization. Factors associated with duration of ventilator support and length of stays were shown in Table 6.

TABLE 6. Factors associated with ventilator support and length of stays.

Factors associated with IMV duration	Days change in ventilator support	95%CI	*P*-value
Neonatal Factors			
Birth weight (per each 100 gram)	0.1	(-1.0) – 1.2	0.804
Gestational age (per each week)	0.4	(-1.3) – 2.1	0.623
Body type (SGA)	8.3	(-4.9) – 21.5	0.214
Completed antenatal steroid	-0.1	(-4.5) – 4.3	0.959
Surfactant Factors			
Early SRT	0.6	(-7.8) – 9.0	0.888
Surfactant characteristic (no budesonide)	-3.2	(-13.2) – 6.7	0.516
SRT technique of first dose (INSURE)	0.8	(-6.3) – 7.9	0.826
Number of surfactant (per each dose)	7.1	(-3.9) – 18.3	0.201
Dosage of first surfactant (per each 10 mg/kg)	0.1	(-1.1) – 1.3	0.835
Postnatal Complications			
Ventilator associated pneumonia	19.8	11.3 – 28.3	<0.001*
Septicemia	13.4	4.4 – 22.4	0.004*
Necrotizing enterocolitis	-3.5	(-12.7) – 5.6	0.433
Air leak syndrome	0.5	(-7.3) – 8.3	0.896
Hemodynamic significant PDA	1.9	(-5.3) – 9.2	0.590
Factors associated with NIV duration	**Days change in ventilator support**	**95%CI**	***P*-value**
Neonatal Factors			
Birth weight (per each 100 gram)	-3.2	(-4.8) – (-1.6)	<0.001*
Gestational age (per each week)	-4.1	(-6.6) – (-1.4)	0.003*
Body type (SGA)	4.1	(-14.6) – 22.8	0.663
Completed antenatal steroid	-6.9	(-13.4) – (-0.5)	0.035*
Surfactant Factors			
Early SRT	8.3	(-3.1) – 19.7	0.151
Surfactant characteristic (no budesonide)	-2.6	(-16.9) – 11.6	0.711
SRT technique of first dose (INSURE)	2.6	(-4.6) – 9.9	0.473
Number of surfactant (per each dose)	19.9	2.6 – 37.3	0.025*
Dosage of first surfactant (per each 10 mg/kg)	-1.3	(-3.1) – (-0.4)	0.150
Postnatal Complications			
Ventilator associated pneumonia	3.9	(-8.4) – 16.2	0.527
Septicemia	4.9	(-9.3) – 19.1	0.497
Necrotizing enterocolitis	0.8	(-11.2) – 12.8	0.894
Air leak syndrome	-8.2	(-20.8) – 4.4	0.198
Hemodynamic significant PDA	13.1	1.7 – 24.5	0.025*

TABLE 6. Factors associated with ventilator support and length of stays. (Continued)

Factors associated with length of stays	Days change in ventilator support	95%CI	*P*-value
Neonatal Factors			
Birth weight (per each 100 gram)	-3.5	-5.2 – (-1.8)	<0.001*
Gestational age (per each week)	-5.4	-8.0 – (-2.7)	<0.001*
Body type (SGA)	13.2	-7.1 – 33.5	0.199
Completed antenatal steroid	-3.7	-10.8 – 3.2	0.284
Surfactant Factors			
Early SRT	11.7	-0.6 – 24.0	0.063
Surfactant characteristic (no budesonide)	4.8	-10.6 – 20.3	0.534
SRT technique of first dose (INSURE)	-1.9	-9.8 – 5.9	0.626
Number of surfactant (per each dose)	27.8	8.9 – 46.6	0.011*
Dosage of first surfactant (per each 10 mg/kg)	0.4	-1.6 – 2.3	0.702
Postnatal Complications			
Ventilator associated pneumonia	16.9	3.5 – 30.3	0.020*
Septicemia	21.4	5.9 – 36.9	0.008*
Necrotizing enterocolitis	-4.7	-17.7 – 8.3	0.470
Air leak syndrome	-13.0	-26.4 – 0.4	0.056
Hemodynamic significant PDA	12.5	0.2 – 24.9	0.047*

Abbreviations: IMV = invasive mechanical ventilator, 95%CI = 95% confidence interval, * = statistically significant, SRT = surfactant replacement therapy, NIV = non-invasive mechanical ventilator, PDA = patent ductus arteriosus

DISCUSSION

Several studies showed that E-SRT could benefit neonates with RDS more than L-SRT in shortening the duration of IMV and NIV.[4,5] A 2012 Cochrane review also concluded that E-SRT could reduce risk for air leak syndrome, BPD and mortality rate.[15] However, this study demonstrated that neonates who received E-SRT had longer duration of IMV than neonates receiving L-SRT although not statistically significant. Similarly, duration of NIV, duration of oxygen usage, oxygen usage at 28 days and oxygen usage at 36 weeks PMA were also longer among neonates in E-SRT group but also not statistically significant. The reason for these conflicting outcomes could be explained by the lower GA and BW and higher rates of hsPDA, septicemia and VAP among neonates in E-SRT group which could be associated with more severe RDS with critically ill conditions prompting immediate intubation and SRT while neonates in L-SRT group could be more medically stable and received SRT later when RDS had progressed. Clinical severity of neonates in E-SRT group could be noted with more neonates received multiple doses of SRT than neonates in L-SRT group. Likewise, this also reflected in the significantly lower number of neonates in E-SRT group with IMV-free, NIV-free, and oxygen-free days at age of 60 days than L-SRT group.

This study found that factors independently associated with longer duration of respiratory support were having VAP, and septicemia. VAP is a common complication among preterm neonates causing inflammation and injury to the lungs while septicemia causes systemic inflammatory response syndrome leading to inflammatory lung injury. Additionally, neonates with VAP and septicemia are likely to be medically unstable requiring prolonged IMV support which could directly injure the lungs by volutrauma and barotrauma leading to BPD.[16,17] Multiple doses of SRT was shown to help reducing mortality and respiratory supports among neonates with severe RDS.[18] In this study, most of neonates who received multiple doses of SRT were in E-SRT group who had lower GA and BW and could possibly have more severe RDS leading to the requirement of multiple doses of SRT.

These neonates could have other pathogenic mechanisms, such as infection, causing surfactant inactivation and, therefore, requiring subsequent SRT.[19] This study also found that neonates in E-SRT group had higher rate of VAP and septicemia which could better explain the longer duration of IMV support rather than by having multiple doses of SRT.

In terms of NIV, multiple factors were associated with longer duration of NIV support such as number of SRT dose and hsPDA similar to previous studies that demonstrated hsPDA could contribute to longer duration of IMV, NIV and oxygen supplements.[20,21] Higher number of SRT dose was associated with more severe RDS which could also lead to longer duration of IMV, NIV, length of stays. Although length of stays did not differ significantly between each group, factors that could prolonged hospitalization were VAP, septicemia, and hsPDA according to this study.

After adjusted for sex, GA and BW, there was no significant differences about IVH, air leak syndrome, hsPDA, septicemia, VAP, NEC, and BPD between neonates in E-SRT and L-SRT groups which mean that timing of SRT was not associated with adverse outcomes. Neonates in E-SRT group also had significantly more IMV support before SRT than L-SRT group. It is known that IMV is associated with lung injury due to volutrauma and barotrauma leading to BPD. At our institution, pressure-controlled with volume guarantee (VG) for conventional IMV and HFOV with VG were used in all neonates who were intubated to minimized fluctuation of tidal volume, and thus, minimizing volutrauma effect from IMV. This could explain the BPD rate among neonates in both group which did not differ significantly. However, ROP rate was higher among neonates in E-SRT group which could be caused by the longer duration of IMV, NIV and oxygen supplement.

Another finding from this study was the mortality rate which was significantly higher among neonates in E-SRT group. However, causes of death were not related to RDS i.e., lung hypoplasia, severe IVH and septicemia, which were mainly associated with prematurity and was not treatable with SRT. There were no significant differences in characteristics of neonates in E-SRT group who survived or died in terms of sex, GA and BW.

This study demonstrated that VAP and septicemia were important risk factors that could prolong duration of IMV while timing of SRT did not show to be associated with. Additionally, VAP and septicemia were also associated with longer length of stays. Strict protocol to prevent VAP and septicemia should be implemented to help shorten the need for ventilator support and hospital stays. Additionally, this study found that timing of SRT did not associate with prolonged duration of ventilator support or other adverse outcomes. Therefore, in resource-limited settings it would be logical to wait and selectively provide SRT to neonates who are in need of the treatment to maximize SRT effectiveness and to avoid unnecessary SRT with less concern for adverse outcomes. Treating hsPDA may also reduce duration of NIV and length of stays.

Limitations

Several limitations were noted in this study. The number of neonates receiving SRT was relatively small and the design of the study was retrospective, therefore, the results might be affected by confounding factors. There were no standard criteria for SRT or extubation causing treatment variation among neonates. Surfactant types and doses were also varied among neonates. Recommended dose for poractant alfa was 200 mg/kg and for beractant was 100 mg/kg but due to cost constrain, majority of neonates had received lower dose than the recommendation. A prospective randomized control trial study with larger population and standard criteria for SRT, dosage of surfactant and extubation criteria could provide more accurate results.

CONCLUSION

Neonates who received E-SRT had longer duration of IMV than neonates who received L-SRT but not statistically significant. Also, there were no significant differences in other neonatal outcomes between each group. Adverse outcomes were likely to be related to GA and BW rather than timing of SRT. VAP and septicemia were major factors associated with prolonged ventilator support and adverse neonatal outcomes, thus, emphasis on preventing VAP and septicemia could be beneficial for neonates.

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Conflicts of interest statement

Authors had no conflict of interest to declare.

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