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Neurodevelopmental Outcomes at 2 Years in Preterm Neonates with Respiratory Distress: Impact of Exogenous Surfactant

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ABSTRACT

Background: Improvement in tertiary neonatal care of private and public sectors in India has resulted in increased survival of extreme pre-term, very pre-term and early/moderate pre-term neonates but with more associated morbidity like neurodevelopmental delay. The commonest immediate complication of pre-term babies is respiratory distress syndrome (RDS) due to endogenous surfactant deficiency. A complete course of antenatal steroids to the mother before pre-term delivery has a proven impact in reducing the severity of RDS in pre-term <34 weeks of gestation.

Methods: This was a population-based prospective analytical study conducted by random enrollment of pre-term neonates <34 weeks and >24 weeks of gestation with respiratory distress admitted and discharged from special newborn care units (SNCU)/ neonatal intensive care units (NICU) of Kottayam district and attending for follow up within 3 months of birth. The study was conducted over 6 years (2017-2023). Preterm babies with known congenital anomalies, congenital birth defects, dysmorphic and other genetic syndromes were excluded from the study.

Results: Total pre-term <34 weeks neonates with respiratory distress admitted in SNCU/NICU and followed up to corrected 2 years of age were 150 of which 79 belonged to early rescue surfactant group, 22 to late rescue surfactant group and 49 to Nil surfactant group. The mean value of the total and individual domain-wise neurodevelopmental status scores was significantly higher for the early rescue surfactant group compared to the Nil surfactant and late surfactant groups.

Conclusions: Early rescue exogenous surfactant treatment in preterm newborns improves neurodevelopment at corrected 2 years compared to late rescue and nil surfactant administration.

Key-words: Early rescue surfactant, Late rescue surfactant, Neurodevelopmental outcome, Preterm less than 34 weeks

INTRODUCTION

Surfactant deficiency due to immaturity of the lung parenchyma is a major disorder in premature births less than 34 weeks of gestation leading to neonatal respiratory distress syndrome (RDS) as well as related complications. Major interventions to reduce the impact of this include the use of antenatal steroids, early continuous positive airway pressure (CPAP) ventilation immediately after delivery and exogenous surfactant administration [1].

Various studies have demonstrated the usefulness of these interventions in reducing the morbidity and mortality associated with respiratory distress syndrome beyond doubt. However, the optimal timing, indication and route of administration of exogenous surfactant is a matter still under debate [2]. Prophylactic surfactant is the method in which all preterm neonates are given

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exogenous surfactant before the onset of neonatal respiratory distress anticipating respiratory distress syndrome through the endotracheal route [1]. Early rescue surfactant is the administration of surfactant through the endotracheal route to preterm neonates with RDS within 2 hours of delivery and late rescue surfactant administration when it is given after 2 hours of delivery when there is the deterioration of RDS [1].

The conventional route of administration of exogenous surfactant is the endotracheal route. Recently alternative methods of administration of surfactant are being tried which include less invasive surfactant administration (LISA) to trachea using small feeding tubes/ thin catheters without endotracheal intubation, nasopharyngeal nebulisation or laryngeal mask airway [2-4].

Natural exogenous surfactants are generally preferred over synthetic surfactants [1,5]. All the preterm neonates enrolled for the present study had received natural exogenous surfactant through the endotracheal conventional route. INSURE is the method in which intubation and administration of surfactant are followed by extubation and CPAP [10]. Many randomized trials have demonstrated the effectiveness of early surfactant therapy along with early CPAP in reducing invasive ventilatory support, decreasing the incidence of air leak syndromes and reducing the occurrence of bronchopulmonary dysplasia (BPD [6-10].

MATERIALS AND METHODS

Research Design- This population-based prospective observational analytic study was conducted over 6 years from 2017 to 2023. Detailed perinatal history and indication and timing and mode of administration of natural exogenous surfactant were recorded. Based on the data surfactant status was defined as three groups (1) early rescue surfactant (2) late rescue surfactant and (3) nil surfactant. The sample size was determined using the Cochran formula assuming the prevalence of preterm deliveries with neonatal respiratory distress as 10% of total deliveries and found to be 138 at 95% confidence interval with 5% precision. Random enrolment started in 2017 and continued over 2 years and the final neurodevelopmental assessment was done at respected corrected 2 years of age.

Neurodevelopmental assessment was done using Bayley scales of infant and toddler development edition-3 (BSID-111) of cognitive, gross and fine motor, receptive and expressive communication, and social-emotional domains. All domains except social-emotional were assessed by the principal investigator directly and the social-emotional domain was assessed using the English/Malayalam version of the questionnaire, with the help of parents.

Inclusion criteria

- Preterm neonates less than 34 weeks of gestation and more than 24 weeks.
- Admitted for neonatal respiratory distress and discharged from special newborn care unit (SNCU)/neonatal intensive care unit (NICU)
- Followed up within 3 months of delivery were randomly enrolled for the study.

Exclusion criteria

- Neonates outside the 24 to 34-week gestational range.
- Neonates without respiratory distress or those who did not follow up within the required period.

Statistical Analysis- Statistical techniques such as measures of central tendency, standard deviation, coefficient of skewness and kurtosis, parametric tests such as one-way analysis of variance (ANOVA) and bonferroni post hoc test were employed for analysing the data.

Ethical Approval- Approval for the study was obtained from the institutional ethics committee, School of Behavioural Sciences, Mahatma Gandhi University, Kottayam, Kerala, India dated on 22-09-2017.

RESULTS

Table 1 shows that mean total and domain-wise, cognitive, language, motor, social-emotional neurodevelopmental status scores values, at corrected 2 years of age, are highest for pre-term (<34 weeks) early rescue surfactant group (1) babies and the lowest for preterm (<34 weeks) late rescue surfactant group (2) babies and intermediate value for nil surfactant status (3) babies.

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Table 1: Mean values and standard deviations of total and domain-wise neurodevelopmental status scores, of different groups of pre-term (<34 weeks) babies at corrected 2 years of age, concerning their surfactant administration status.

Neurodevelopmental status	Groups- surfactant status	N	Mean	SD
Total	1. Early rescue	79	352.72	28.38
	2.Late rescue	22	304.99	38.79
	3.Nil	49	334.12	31.69
Cognitive	Groups- surfactant status	N	Mean	SD
	1. Early rescue	79	86.08	7.28
	2.Late rescue	22	75.45	7.11
	3.Nil	49	81.94	7.42
Language	Groups- surfactant status	N	Mean	SD
	1. Early rescue	79	92.35	7.98
	2.Late rescue	22	82.18	9.33
	3.Nil	49	88.24	9.99
Motor	Groups- surfactant status	N	Mean	SD
	1. Early rescue	79	87.96	8.22
	2.Late rescue	22	71.50	13.88
	3.Nil	49	83.22	10.50
Social - Emotional	Groups- surfactant status	N	Mean	SD
	1. Early rescue	79	86.33	9.63
	2.Late rescue	22	75.45	7.70
	3.Nil	49	80.71	8.48

Table 2 summary of one-way ANOVA shows that there are significant differences in mean values of total and domain-wise, cognitive, language, motor, social-emotional neurodevelopmental status scores of different groups of pre-term (<34 weeks) babies at corrected 2 years of age for their surfactant administration status (p-values 0.000).

Table 2: Summary of one way analysis of variance of total and domain wise neuro developmental status scores of pre term (<34 weeks) babies at corrected 2 years of age, concerning their surfactant status.

Total	Source of variation	Sum of squares	df	Mean square	F-value	p-value
	Between groups	42035.92	2	21017.96	22.40	0.000
	Within groups	137938.46	147	938.36		
	Total	179974.38	149			

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Cognitive	Source of variation	Sum of squares	df	Mean square	F	p
	Between groups	2051.02	2	1025.51	16.90	0.000
	Within groups	8919.82	147	60.68		
	Total	10970.84	149			
Language	Source of variation	Sum of squares	df	Mean square	F	p-value
	Between groups	1899.03	2	949.59	12.05	0.000
	Within groups	11584.41	147	78.81		
	Total	13483.44	149			
Motor	Source of variation	Sum of squares	df	Mean square	F	p-value
	Between groups	4707.08	2	2353.54	23.70	0.000
	Within groups	14600.92	147	99.33		
	Total	19308.00	149			
Social - Emotional	Source of variation	Sum of squares	df	Mean square	F	p-value
	Between groups	2882.60	2	1191.30	14.68	0.000
	Within groups	11930.90	147	81.16		
	Total	14313.50	149			

Table 3 pair-wise comparison shows that the preterm (<34 weeks) early surfactant group(1) has a significantly high mean value of total neurodevelopmental status scores at corrected 2 years compared to the late rescue surfactant group (2) and nil surfactant group (3) babies. Late rescue surfactant group (2) has a significantly lower mean value of total neurodevelopmental scores at corrected 2 years of age, compared to nil surfactant group (3) babies (p-values 0.00).

Table 3: Bonferroni test for pair wise comparison, of total neuro developmental status scores of pre term (<34 weeks) babies at corrected 2 years of age, concerning their surfactant status.

Pair	Mean	Mean difference	p-value
1.Eary rescue 2.Late rescue	352.72 304.99	48.13	0.000
1.Early rescue 2.Nil	352.72 334.12	18.60	0.003
1.Late rescue 2.Nil	304.99 334.12	-29.53	0.001

Table 4 pair-wise comparison shows that pre-term (<34 weeks) early rescue surfactant group (1) babies have significantly high mean cognitive score values at corrected 2 years of age compared to pre-term (<34 weeks) late rescue surfactant group(2) and nil surfactant group. Pre-term (<34 weeks) late surfactant group (2) had significantly low mean cognitive score value compared to nil surfactant group (3) babies (p-values 0.00, 0.01, and 0.00, respectively).

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Table 4: Bonferroni test for pair-wise comparison of cognitive scores, of different groups of pre-term (<34 weeks) babies, at corrected 2 years of age, concerning their surfactant status.

Pair	Mean	Mean difference	p-value
1.Eary rescue 2.Late rescue	86.08 75.45	10.63	0.000
1.Early rescue 2.Nil	86.08 81.94	4.14	0.012
1.Late rescue 2.Nil	75.45 81.94	-6.49	0.004

Table 5 pair-wise comparison shows that pre-term (<34 weeks) early rescue surfactant group (1) babies have significantly high mean language score values at corrected 2 years of age compared to late surfactant group (2) and nil surfactant group (3) babies. Pre-term (<34 weeks) late surfactant group (2) babies have lower mean language score values compared to nil surfactant group (3) babies (p-values 0.00, 0.03, and 0.02, respectively).

Table 5: Bonferroni test for pair-wise comparison of language scores, of different groups of pre-term (<34 weeks) babies, at corrected 2 years of age, for their surfactant status.

Pair	Mean	Mean difference	p-value
1.Eary rescue 2.Late rescue	92.35 82.18	10.17	0.000
1.Early rescue 2.Nil	92.35 88.24	4.10	0.036
1.Late rescue 2.Nil	82.18 88.24	-6.07	0.026

Table 6 pair-wise comparison shows that pre-term (<34 weeks) early surfactant group (1) babies have significantly higher mean motor score values at corrected 2 years of age, compared to late surfactant group (2) and nil surfactant group (3) babies. Pre-term (<34 weeks) late surfactant group (2) babies have significantly low mean motor score values compared to the nil surfactant group (30) babies (p-values 0.00, 0.03, and 0.00, respectively).

Table 6: Bonferroni test for pair-wise comparison of motor scores, of different groups of pre-term (<34 weeks) babies, at corrected 2 years of age, concerning their surfactant status.

Pair	Mean	Mean difference	p-value
1.Eary rescue 2.Late rescue	87.96 71.50	16.46	0.000
1.Early rescue 2.Nil	87.96 83.22	4.74	0.030
1.Late rescue 2.Nil	71.50 83.22	-11.72	0.000

Table 7 pair-wise comparison shows that mean value social-emotional scores of pre-term (<34 weeks) early surfactant group (1) babies, at corrected 2 years of age, are significantly higher than that of pre-term (<34 weeks) late surfactant group (2) and nil surfactant group (3) babies (p-values 0.00, and 0.00). There is no significant difference in the mean values of late rescue surfactant group (2) and nil surfactant group (3) babies even though the mean value of late surfactant group babies appears to be low.

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Table 7: Bonferroni test for pair-wise comparison of social-emotional scores, of different groups of pre-term (<34 weeks) babies at corrected 2 years of age, concerning their surfactant status.

Pair	Mean	Mean difference	p-value
1.Eary rescue 2.Late rescue	86.33 75.45	10.88	0.000
1.Early rescue 2.Nil	86.33 80.71	- 5.62	- 0.002
1.Late rescue 2.Nil	75.45 80.71	-5.26	0.073

DISCUSSION

Many perinatal interventions are being undertaken to reduce neonatal morbidity and mortality, especially related to preterm neonates. Around 10% of total deliveries belong to a preterm group in middle and low-income group countries [7,8]. Antenatal interventions to reduce neonatal mortality and morbidity include antenatal steroids and magnesium sulphate administration. Major post-natal interventions include early respiratory support with continuous positive pressure ventilation (CPAP), and exogenous surfactant administration [9]. The conventional method of administration of exogenous surfactant is through the endotracheal tube. Exogenous surfactant is proven to be associated with a decrease in ventilatory support, pulmonary air leak syndromes and bronchopulmonary dysplasia (BPD) [5,10]. Studies related to long-term neurodevelopmental outcomes of preterm babies to surfactants are scanty. Prophylactic surfactants for preterm neonates are not being practised at the present stage [1,11]. Surfactant to preterm neonates with RDS given within 2 hours of delivery is referred to as early rescue surfactant and when it is given after 2 hours, it is referred to as late rescue surfactant [1].

In the present study, 150 preterm neonates belonged to 3 groups, (1) early rescue, (2) late rescue surfactant and (3) nil surfactant groups [5]. All surfactant babies included in the study belonged to the endotracheal administration method. Neurodevelopmental outcomes of these 3 groups at corrected 2 years of age were assessed using Bayley scales of infant and toddler development (BSID-111). Low values of means of neurodevelopment were observed for the late rescue surfactant and nil surfactant group compared to the early surfactant group.

One-way analysis of variance (ANOVA) was suggestive of significant differences between means of 3 groups of preterm babies of total and domain-wise neurodevelopmental scores at corrected 2 years of age.

Bonferroni ad hoc test of pair-wise comparison showed that total, cognitive, communication, motor and social-emotional scores at corrected 2 years of age were significantly higher for the early rescue surfactant group compared to the late rescue and nil surfactant groups of preterm babies. Total and domain-wise neuro developmental mean scores were significantly lower for the late rescue surfactant group compared to the nil surfactant group of children at their corrected 2 years of age. This is found to be a significant finding related to the usefulness of late surfactant administration compared to nil surfactant group in improving the neuro developmental outcome at corrected 2 years of age. Further studies are warranted to confirm the association of late rescue surfactant administration and low mean neurodevelopmental scores, compared to early rescue surfactant and nil surfactant groups, at their corrected 2 years of age.

Improved neurodevelopmental outcomes of preterm less than 34 weeks and more than 24 weeks of gestation of early rescue surfactant group babies may be attributed to the decrease in the severity of RDS, air leak syndromes and intracranial hemorrhage among this group compared to the nil surfactant group of babies.

One study conducted to determine the neurodevelopmental outcome at one year of age in preterm babies, who received early surfactant in one group and selective late surfactant in another group didn't show any significant difference [12]. Another study was that early Surfactant administration given to preterm neonates with RDS requiring assisted ventilation

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resulted in decreased risk of pulmonary injury like pneumothorax and pulmonary interstitial emphysema, decreased risk of neonatal morbidity and chronic lung disease compared with neonates who received surfactant as late rescue when there was worsening of RDS (5). Irreversible/partially reversible changes occurring in multiple organs of the body due to persistent hypoxia and ischemia may be the probable reasons for the decreased efficacy of late rescue surfactant administration in preventing immediate complications like air leak syndromes, neonatal morbidity and chronic lung disease (bronchopulmonary dysplasia) as depicted by this study. The same reasons may result in lower neurodevelopmental outcomes of preterm babies less than 34 weeks gestation with RDS and late rescue surfactant administration group compared to preterm less than 34 weeks of gestation with RDS and early rescue surfactant administration group, at corrected 2 years of age [13].

CONCLUSIONS

The study shows that preterm less than 34 weeks of gestation with RDS and early rescue exogenous surfactant administration are associated with significantly better total and domain-wise neurodevelopmental outcomes, at their corrected 2 years of age compared to the nil surfactant and late surfactant groups of preterm neonates with RDS, at corrected 2 years of age. However, in the present study, preterm babies less than 34 weeks of gestation with RDS and late rescue surfactant were found to be associated with significantly lower total and domain-wise neurodevelopmental outcomes compared to preterm babies less than 34 weeks of gestation with RDS and nil surfactant. So according to the present study, early exogenous surfactant administration should be preferred over late surfactant administration in preterm neonates less than 34 weeks of gestation with RDS for a better total and domain-wise neurodevelopmental outcome of these groups of babies at their corrected 2 years of age.

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