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SURVIVAL OUTCOME COMPARISON BETWEEN EARLY AND LATE OXYGEN THERAPY AMONG PRETERM NEONATES SUFFERING FROM RESPIRATORY DISTRESS SYNDROME IN IBN AL-BALADI HOSPITAL / BAGHDAD- IRAQ

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ABSTRACT

Prematurity and RDS largely contribute to early neonatal morbidity and mortality. With adequate antenatal steroid and early CPAP, early oxygen therapy improves survival outcome. The current study aimed to compare survival outcome of oxygen therapy with respect to timing of its administration (i.e. early within two hours of life and late after 2 hours), different birth weight and different gestational age. This 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 oxygen therapy (within 2 hours after birth). Oxygen was delivered and only those who required further respiratory support were ventilated. Records on birth weight, gestational age, and timing of therapy (early/late), duration of ventilation, sepsis, complications, and survival/death outcome were collected and data was analyzed using SPSS version 20. Out of 80 neonates (39 males, 41 female), 36 received early oxygen therapy and 44 obtained it late. Although high mortality was observed with both early (32.8%) and late therapy (67.2%), there was significantly higher survival with early therapy (p=0.02). Though no statistical differences of outcome were observed with different GA and BW in study groups; however irrespective of timing of therapy, higher mortality occurred in lower BW/GA subgroups with least survival among extremely preterm <27wks (p=0.005) and ELBW<1000gm (p=0.001). No difference was seen for need of intubation/ventilation in early and late groups (p=0.831). It can be concluded that early oxygen administration improved survival with minimal complications in RDS except for extremely premature/LBW babies.

KEYWORDS: Preterm neonates, RDS, Oxygen 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 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.

Oxygen therapy have markedly improved the survival of preterm, LBW, and VLBW infants, and have resulted in

reduced neonatal and infant mortality.[10] The timing of oxygen 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]

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

MATERIALS AND METHODS

The present prospective interventional study (Randomized clinical trial, open) was designed and performed in the NICU (neonatal intensive care unit) of Ibn Al-Baladi hospital in Baghdad / Iraq during the period from October 2017 to October 2018 on 80 neonates with respiratory distress syndrome. It included babies between 24-28 weeks of gestational age and 28-34 weeks babies with clinical RDS. The following neonates were excluded from our study: 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.

Statistical analysis

Data were interpreted and expressed as percentage and mean ± S.D. Kolmogorov-Smirnov analysis was performed for checking normality 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 V20 was used to perform the statistical analysis.

RESULTS

Out of 80 preterm newborns enrolled, 39 were male and 41 female. Of those, 36 patients receiving early oxygen therapy (within < 2 hours of birth), male and female were equal; while among 44 late therapy recipients, around 57.5% were females and 42.5% were males.

Table (1): Gender distribution of patients in study groups.

			Time of oxygen delivery		Total	P value
			EARLY	LATE		
Gender	Female	Count	18	23	41	0.928
		% within	50.0%	57.5%	51.3%	
	Male	Count	18	21	39	
		% within	50.0%	42.5%	48.7%	
Total		Count	36	44	80	
		% 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 eighty eligible preterm between 24-34 weeks gestational age and birth weight above 650 grams and having risks or clinical features of RDS. 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.

	Oxygen delivery	Number	Mean	SD	P value
Weight (Kg)	Early	36	1.1845	0.3478	0.862
	Late	44	1.1987	0.3772	
Gestational age (Weeks)	Early	36	30.2784	2.5545	0.400
	Late	44	29.7951	2.5345	

Overall patient outcome indicated that only 19 (23.8%) babies had intact survival after oxygen therapy and 61 (76.2%) succumbed (to RDS and/or other co-morbidities) in this study. Significantly more deaths occurred among subjects receiving late oxygen therapy i.e. 41/61 (67.2%) compared to 20 of total 61 deaths (32.8%) among early therapy group (p=0.0128).

Although no statistically significant difference was obtained for survival and death outcomes between two study groups (based on oxygen timing) with respect to different subgroups of gestational age (p=0.50) {see table 3} and birth weight (p=0.50) {table 4}.

Table (3): Outcome after early and late oxygen therapy in different gestational age sub-groups.

Gestational age		Outcome					
		Death			Improve		
		Time of oxygen delivery		Total	Time of oxygen delivery		Total
		Early	Late		Early	Late	
	count	**3**	**8**	**11**	**0**	**0**	**0**
24-27	%	27.3%	72.7%	100.0%	0.0%	0.0%	0.0%
	count	10	25	35	3	1	4
28-30	%	28.6%	71.4%	100.0%	75.0%	25.0%	100.0%
	count	7	8	15	10	5	15
31-34	%	46.7%	53.3%	100.0%	66.7%	33.3%	100.0%
	count	20	41	61	13	6	19
Total	%	32.8%	67.2%	100.0%	68.4%	31.6%	100.0%

Table (4): Outcome after early and late oxygen therapy in different birth weight sub-groups.

			Death			Improve		
			Time of oxygen delivery		Total	Time of oxygen delivery		Total
			Early	Late		Early	Late	
Weight (Kg)	0.650-0.850	count	6	7	13	1	0	1
		%	46.2%	53.8%	100.0%	100.0%	0%	100.0%
	0.851-1.0	count	3	5	8	2	0	2
		%	37.5%	62.5%	100.0%	100.0%	.0%	100.0%
	1.01-1.2	count	3	14	18	0	0	0
		%	16.7%	83.3%	100.0%	0%	0%	0%
	1.21-1.5	count	7	13	19	6	5	11
		%	36.8%	63.2%	100.0%	54.5%	44.5%	100.0%
	>1.5	count	1	2	3	4	1	5
		%	33.3%	66.7%	100.0%	80.0%	20.0%	100.0%
Total		count	20	41	61	13	6	19
		%	32.8%	67.2%	100.0%	68.4%	31.6%	100.0%

If we discard poor outcomes of extremely LBW/premature subgroups and then compare overall survival benefits, then it definitely reveals significantly favorable outcome with early oxygen therapy. Thus, it seems, survival outcome might not be solely dependent on oxygen 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 oxygen delivery.

Birth weight (in grams)	Improved (N)	Death (N)	Total (N)	Mortality (%)	Survival (%)
650-850	1	13	14	92.8%	7.2%
851-1000	2	8	10	80.0%	20.0%
1001-1200	0	18	18	100.0%	0%
1201-1500	11	19	30	63.3%	36.7%
>1500	5	3	8	37.5%	62.5%
TOTAL	19	61	80	-	-

(P value = 0.001)

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

Birth weight (in grams)	Improved (n)	Death (n)	Total (n)	Mortality (%)	Survival (%)
25-27	0	11	11	100%	0%
28-30	4	35	39	89.7%	10.3%
31-34	15	15	30	50.0%	50.0%
TOTAL	19	61	80	-	-

(P value = 0.005)

Table 5 and 6 reveal significant difference on mortality rates between various birth weight bands {92.8-100.0% for 650-1200gms, while 37.5-63.3% for >1200gm; p=0.001} and gestation age subgroups {all died with 24-27 weeks prematurity, while less mortality(89.7%) in 28-30wks, and least 50.0% was seen in 31-34wks maturity groups; p=0.005}.

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 oxygen irrespective of its timing of administration.

Out of 80 subjects, 67(83.7%) required ventilation and 13 (16.3%) did not. There was no significant difference noted between two groups with reference to need for ventilation post oxygen therapy (p=0.831) {see table 7}.

Table (7): Comparison of ventilation between study groups.

			Time of oxygen delivery		Total	P value
			EARLY	LATE		
Ventilation	Absent	Count	7	6	13	0.831
		%	19.6%	13.0%	16.3%	
	Present	Count	37	30	67	
		%	55.2%	44.8%	83.7%	
Total		Count	44	36	80	
		%	100.0%	100.0%	100.0%	

DISCUSSION

Respiratory distress syndrome has been recognized as the most common co-morbidity of prematurity. Oxygen therapy had been an established effective and safe therapy for prematurity-related RDS 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 oxygen 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 oxygen administration in a public sector tertiary setting with resource constraints and multiple risk factors for mortality in addition to prematurity with RDS alone. Secondarily, one major objective was to compare mortality between different birthweight and gestational prematurity subgroups with reference to timing (early/late) of oxygen administration.

A total of 80 neonates between 24-34 weeks of gestational age and birth weight >650gms with clinical features/risks of RDS had been enrolled, of which 39 were male and 41 were female. Thirty-six neonates received early therapy and 44 could be given late oxygen therapy.

With respect to primary outcome our study showed comparatively higher survival rate in patients receiving early oxygen therapy compared to late rescue therapy (68.4% vs 31.6%) and vice versa for the mortality rates with higher mortality after delayed intervention (67.2% vs 32.8%), p value =0.0128.

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 {92.8-100.0% for 650-1200gms, while 37.5-63.3% for >1200gm; p=0.001} and gestation age subgroups {all died with 24-27 weeks prematurity, while less mortality(89.7%) in 28-30wks, and least 50.0% was seen in 31-34wks maturity groups; p=0.005}. 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.

Regarding need of ventilation, out of 80 neonates, 67 required mechanical ventilation post oxygen therapy and 13 maintained well on minimal nasal CPAP support for 6-24 hours. There was no statistically significant difference in terms of immediate need of re-intubation and mechanical ventilation in two study groups, p value=0.831). Previous two studies by Jayachandra et al and Kandraju 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]

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]

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