Noninvasive Modes of Respiratory Support for the Management of Respiratory Distress Syndrome a Comparative Study in a Resources Limited Setting

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Abstract

Background: Respiratory distress syndrome (RDS) is mainly a disease of prematurity; noninvasive respiratory support has become the preferred method of management.

Objectives: study the demographic characteristics of preterm infants admitted to the neonatal unit (NNU)diagnosed with RDS and compares the effectiveness of three modes of noninvasive respiratory support.

Patient and methods: An observational comparison study of 545 newborns delivered at the Al Yarmouk teaching hospital, admitted to NNU with clinical and radiological diagnosis of RDS managed with three modes of noninvasive respiratory support from January2013 -December 2014.

Results:

Primary outcome: treatment failure ended with mechanical ventilation in the A group 49/200(24.5%), B group 30/200(17.5%) ,relative risk{CI=0.9937-2.2905(p=0.053)}.

Secondary outcome: hours spent on the nCPAP support , ≤ 72 hours the B group 169/200(84.5%) infants compared to A group 112/200(56%) infants who had not received surfactant, p=0.0001 ; infants from(B group) who spent >72 hr were 31/200(15.5%) compared to A group 88/200(44%), p= 0.0076.

Days of hospitalization : a significant less days of hospitalization were spent by the B group versus A group (P=<0.0001) ;B group versus group C, (P= 0.0001). Outcome in A group was 60.5%(121\200) infants were discharged well and 39.5%(79/200) passed away during their hospital stay, 73% infants of B group survived (146/200) and 27% died(54/200) while 60% of infants treated with Oxyhood only survived (87/145) and 40% died (58/145).

Conclusion: The INSURE method nCPAP most effective intervention within the settings of our limited resources.

Keywords: Respiratory distress syndrome, Continuous positive airway pressure, Surfactant replacement therapy, preterm.

Introduction :

The global rate of prematurity is estimated to be 9.6% of which 80% occurring in Asia and Africa contributing to 27% of global neonatal deaths; while respiratory distress is the most common symptom in sick newborn and Respiratory distress syndrome (RDS) is mainly a disease of prematurity, there is yet no global data on its occurrence, but preterm birth complication collectively is one of the three leading causes of death in under-five deaths. In Iraq, death during the neonatal period accounted for more than half of under-five children deaths, with 42.3%of neonatal death due to difficulty in breathing .[1-4]

Respiratory distress syndrome (RDS) is observed in prematurely born infants. Surfactant production is insufficient due to the immature development of type II pneumocytes, which begin to produce surfactant at approximately 20 weeks gestation [Insufficient surfactant leads to reduced pulmonary compliance and increased surface tension . This results in increased risk of alveoli collapse at expiration followed by reduction in total surface area for gaseous exchange, as well as the alveolar-capillary diffusion capacity. Hypoxia and hypercapnia develops. The risk and severity of RDS are inversely proportional to the gestational age of the infant at birth Prior to the introduction of surfactant, RDS was considered to be the leading aetiology of mortality in preterm infants ;In 1959 Fujiwara was the first to use it for the treatment of ten preterm babies, and since then it has become a standard therapy for the treatment of RDS. Considering the universal benefits of surfactant replacement therapy (SRT) in the treatment of RDS and its impact on the reduction of neonatal mortality, surfactant preparations were approved and included in the essential drug list (EDL) by the WHO in 2008. Continuous positive pressure ventilation (CPAP) was first introduced in 1971 by Gregory et al for newborns with RDS, the goal of which was to prevent end-expiratory alveolar collapse, reduce the work of breathing and thus better ventilation-perfusion match. [5-12]

This study's aim was explore the demographic characteristics of the enrolled infants to compare three non-invasive modes of RDS management analyzing their primary and secondary outcome contributing to the little available national data concerning RDS and its management in NICU's with limited resources.

Patients and methods:

During a two year time period from the first of January 2013 until the thirtieth of December 2014, an observational comparison study of a total of 545 newborns delivered at the maternity department of Al Yarmouk teaching hospital in Baghdad who were admitted to the Neonatal unit (NNU) with the diagnosis of respiratory distress syndrome and managed according to availability by one three different modes of noninvasive respiratory support.

The demographic characteristics(weight in grams ,gestational age in weeks, mode of

delivery{spontaneous vaginal delivery or cesarean section}, age of the mother) of Infants enrolled in the study were documented categorized into three groups: two hundred infants were treated with bubble nasal continuous positive airway pressure nCPAP *(Fischer & paykel, Inc. Auckland, New Zealand)* only(Group A); and two hundred infants were intubated followed by administering the surfactant *(Survanta, bovine surfactant ABBOTT)* then extubated to nCPAP (the INSURE method) according to the Danish –Sweden multicenter study group) (Group B), these two groups were compared to an earlier group of patients one hundred forty five infants treated with oxyhood only respiratory support before the availability of the surfactant and NCPAP (Group C).[13,14]

Infants included were those who met the following criteria: gestational ages from 27 to $36^{6\backslash 7}$weeks, gestation which was estimated by first-trimester ultrasound, maternal dates of last menstrual period and clinical assessment after delivery with the new Ballard score. The anticipation of RDS was on the bases of gestational age and the clinical diagnosis of respiratory distress syndrome confirmed by the presence of signs of RDS (tachypnea, grunting, increased work of breathing: nasal flaring, retraction of intercostal and subcostal recession), and confirmed by signs of cyanosis and pallor and lethargy, disinterest in feeding ,apnea , further confirmation was by radiological features of reticular granular(i.e. ground glass) pattern and air bronchogram. [15,17]

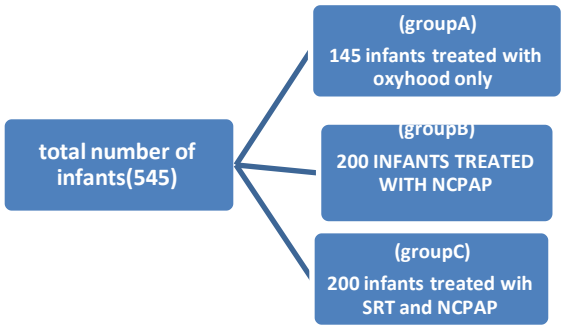
All patients were provided with the basic resuscitation required according to the neonatal resuscitation program [13], positive pressure support with neopuff (Fischer and Paykel) or auto breath (dragger) and aftercare of drying, warmth, intravenous fluids and electrolytes, nutrition and antibiotics according to the unit's protocols. Initial Investigations included: chest x-ray, blood glucose level, complete blood picture, blood culture, transcutaneous oxygen saturation (Spo2); echocardiogram carried out as required; these done to exclude cardiac causes, bacterial pneumonia, sepsis, hypoglycemia and polycythemia as a cause for the respiratory distress.[17]

Infants were observed for the first two hours post delivery ,if RDS was diagnosed the newborn was assigned to either to NCPAP or Surfactant replacement therapy (SRT) followed by NCPAP according to the availability of the surfactant , an early rescue protocol is followed to give beractant surfactant within the first two hours of birth with a single dose of 100mg /kg only because of the limited availability we couldn't administer more than one dose for each patient. The group who received SRT, infants were intubated with the appropriate size of an un-cuffed endotracheal tube with a side port to administer the surfactant then were monitored for spo2 and heart rate, the SRT dose was given in the supine position then immediately put on NCPAP with peak end-expiratory pressure (PEEP) of 5-6 cm H_2O with Fio2 at 40% ,reevaluation after half an hour time to optimize the settings and monitor infants vital signs spo2, and work of breathing. Those requiring higher fio2 than 60% and or work of breathing not settling after the first two hours were transferred to the mechanical ventilator.Exclusion criteria were set as any infant with history of prolonged rupture of membranes >18 hours, suspected chorioamnionitis, lung hypoplasia, congenital heart disease and major congenital anomaly

The primary outcome was assigned to be: treatment failure with a fio2 requirement of more than 60% and excessive work of breathing not settling on NCPAP, infant transferred to mechanical ventilation; pneumothorax diagnosed by clinical suspicion confirmed by x-ray and lastly, Intraventricular hemorrhage diagnosed clinically and confirmed by transfrontal ultrasound.The Secondary outcome was set as follows: hours spent on nCPAP, days of hospital stay, the mortality rate in each group.

Analysis of data was carried out using the available statistical package of SPSS-22 (Statistical Packages for Social Sciences- version 22). (317/58%)versus (228/42%) delivered through spontaneous vaginal delivery . (Table 1).

Data were presented in simple measures of frequency, percentage, mean, standard deviation,



and range (minimum-maximum values).The significance of the difference of different percentages (qualitative data) was tested using Pearson Chi-square test (χ^2-test) with the application of Yate's correction or Fisher Exact test whenever applicable. Pearson correlation was calculated for the correlation between two quantitative variables with its t-test for testing the significance of correlation. Statistical significance was considered whenever the P value was equal or less than 0.05.

Results:

During the study period of two years, a total of four hundred forty five infants born in the maternity department of Al yarmouk teaching hospital, diagnosed clinically and confirmed radiologicaly as cases of respiratory distress, , with gestational age ranging from $27^{0\backslash 7}$ weeks to36weeks$^{6\backslash 7}$, when the NCPAP was available as well as limited supply of beractant surfactant, two hundred infants were treated with NCPAP only(groupA) and two hundred infants treated with surfactant and NCPAP(Group B)and one hundred forty five infants were treated for RDS with oxyhood oxygen therapy only(group C) as the method for respiratory support as it was the only support method available in the beginning of the study, .

The demographic characteristics observed : Out of the total infants studied, 331/60.7% were male infants and 214/39% were females.

The weight characteristics of the three groups were similar, with the SRT group having a lower weight range, when compared to Oxyhood only treated group; the gestational age range was similar in both oxyhood and nCPAP treated infants while in the SRT group infants had a lower gestational age range ; 166/30.4% mothers were primipara and 379/69.5% were multipara , Cesarean section was the dominant method of delivery observed in this group with established RDS with a rate

Primary outcome:

treatment failure that ended with transferring the infant to mechanical ventilation in the nCPAP group 49/200(24.5%), SRT group 30/200(17.5%) ,relative risk{CI=0.9937-2.2905(p=0.053)}.

Pneumothorax diagnosed in NCPAP treated infants were 5/200(2.5%), SRT treated infants were 2/200(1%) and in the oxyhood, treated infants were 2/145 (1.3%),no significant difference was found.(Table2)

Secondary outcome:

hours spent on the non invasive respiratory support were divided into two categories : less or equal to seventy two hours and over seventy two hours ;in the first category ,the B group, 169/200(84.5%) infants compared to 112/200(56%) infant who had not received surfactant(A group), p=0.0001 ; infants from B group who spent >72 hr were 31/200(15.5%) compared to A group 88/200(44%), p= 0.0076.

As for days of hospitalization :In the three categories of equal or less than 3 days, equal or less than 6 days , seven days or more ,a significant less days of hospitalization were spent by the (B) group versus A group (P=<0.0001) and B group versus group, (P= 0.0001);no difference in A group versus C group ,(P=0.453).(Table3

Nasal septal necrosis in the A group was 6/200(3%) and in the B group 4/200(2%).

Outcome in A group was as follows : 60.5%(121\200) infants were discharged well and 39.5%(79/200) passed away during their hospital stay, 73% infants of B group survived (146/200) and 27% died(54/200) while 60% of infants treated with Oxyhood only survived (87/145) and 40% died (58/145).with significant difference in survival in B group compared to infants managed with Oxyhood only therapy while there was no significant difference in survival between A and C groups .

Total Case fatality rate was 38.2%.(Table 3)

Table 1: demographic characteristic of the study group

		Group A		Group B		Group C	
		No	%	No	%	No	%
Weight (grams)	<1000	7	3.5	6	3.0	-	-
	1000-1499	53	26.5	69	34.5	31	21.4
	1500-1999	63	31.5	59	29.5	52	35.9
	2000-2499	49	24.5	41	20.5	44	30.3
	≥2500	28	14.0	25	12.5	18	12.4
	Mean (Range)	1782.9±532.6 (800-3000)		1695.2±542.4 (700-3250)		1851.2±470.2 (1000-3000)	
Gestational age (weeks)	≥28	7	3.5	19	9.5	3	2.1
	≤32	55	27.5	75	37.5	29	20.0
	33-35	116	58.0	93	46.5	98	67.6
	≥36	22	11.0	13	6.5	15	10.3
	Mean±SD(Range)	32.5±2.8 (26-38)		31.6±3.1 (25-38)		33.0±2.4 (27-37)	
Gender	Male	117	58.5	128	64.0	86	59.3
	Female	83	41.5	72	36.0	59	40.7
Mode of delivery	CS	126	63.0	104	52.0	87	60.0
	NVD	74	37.0	96	48.0	58	40.0
Parity	Primipara	43	21.5	89	44.5	34	23.4
	Multipara	157	78.5	111	55.5	111	76.6
Maternal risk factor	Yes	58	29.0	72	36.0		
	No	142	71.0	128	64.0		

Table 2:primary outcome

	Group A		Group B	
	No	%	No	%
Treatment failure requiring mechanical ventilation	49	200	30	200
pnumothorax	5	200	2	200

Table 3: secondary outcome of the three study groups

		Group A (n=200)		Group B (n=200)		Group C (n=154)		Group AxB	Group AxC	Group BxC	P value
		No	%	No	%	No	%				
Hours of NCPAP	≤72	112	56	169	84.5	-	-	-	-	-	0.0001*
	>72	88	44	31	15.5	-	-	-	-	-	0.008*
Hospitalization days	≤3	49	24.5	63	31.5	44	30.3	-	-	-	-
	≤6	45	22.5	81	40.5	28	19.3	-	-	-	-
	≥7	106	53	56	28	73	50.3	-	-	-	-
Outcome	Death	79	39.5	54	27.0	58	40.0	0.008*	0.925	0.011*	-
	Well	121	60.5	146	73.0	87	60.0	-	-	-	-

Statistical analysis

Analysis of data was carried out using the available statistical package of SPSS-22 (Statistical Packages for Social Sciences- version 22).

Data were presented in simple measures of frequency, percentage, mean, standard deviation, and range (minimum-maximum values).

The significance of difference of different percentages (qualitative data) were tested using Pearson Chi-square test (χ^2-test) with application of Yate's correction or Fisher Exact test whenever applicable. Pearson correlation was calculated for the correlation between two quantitative variables with its t-test for testing the significance of correlation. Statistical significance was considered whenever the P value was equal or less than 0.05.

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Discussion:

Respiratory distress is the most common symptom in sick newborns. In Iraq, death during the neonatal period accounted for more than half of under-five children death with the difficulty in breathing is the leading symptom preceding the death event 42.3% .[2,4]

National Data on neonatal mortality rates causes by RDS per se is not available in our country as well as globally ,although in a hospital based study RDS was main cause of mortality and morbidity ; until recently , there were no updated interventions for RDS in our settings except providing oxygen therapy by oxyhood or simple nasal cannula, this stunted level of neonatal care was caused by the burden of a health system damaged by years of embargo and wars causing a very slow diffusion of newer medical technology and therapies that happened over an extended period of time affecting the quality of services we provided compared to neighboring countries; thus we sought to introduce bubble CPAP because it constitutes a potentially better practice for the treatment of neonatal lung disease , as well as the introduction of surfactant replacement therapy .[2,18,19]

There is a limited published experience in Iraq in the field of advanced neonatal respiratory support; we aimed in this study to investigate our own experience in comparing three different modes of non-invasive respiratory support .

The demographic charchtaristics of the cohort of infants diagnosed with RDS showed that the mothers were mainly multipara with a ratio of 1:2, a finding caused by the higher rate of Cesarean section in multipara mothers as well as Cesarean section per se is known to be a risk factor for RDS; there was no significant gender difference between the three groups similar to what was reported by Nakhshab et al and Rojas et al, while males were the dominant gender in an earlier Iraqi study ,as it is known that males are more prone to suffer from RDS due to a later lung maturation . Being a tertiary center many high-risk cases were referred from primary and secondary care centers, Cesarean deliveries were the overall dominant mode of delivery; the gestational ages groups showed a lower mean in the B group (31.6 ±3.1 weeks) of gestation due to the use of surfactant in a lower gestation age as a rescue therapy for RDS, a finding which was not consistent with the study by Nakhshab et al. The mean weight in both groups of A and B were lower than the mean weight of the C group.[25-26]

The primary outcome of treatment failure and the need for mechanical ventilation and it was observed mainly in the A group, 42.5% versus 34% in the B group attributed to the beneficial effect of surfactant therapy similar to two studies.[22,23]

Death was inevitable despite intensive care and surfactant replacement therapy in all groups, thus mortality in the A group infants was higher (39.5%)compared to (27%) in infants treated with the INSURE method, while infants put on Oxyhood therapy had the highest mortality rate, thus infants treated with SRT had the better survival outcome

Conclusion: it was observed that among the three of the noninvasive modes of respiratory support used to manage preterm infants suffering from RDS, SRT followed by extubation to NCPAP therapy was the most practical and effective intervention within the settings of a resource tight NICU of a developing country such as Iraq.

similar to studies by VERDER and ROJAS, while in an Iraqi study by Hussein A. S, established that both were effective .[3,21, 24]

Pneumothorax, intraventricular hemorrhage, and septal erosion although less in the SRT group, all were statistically not significantly similar to other studies. [20- 22]

The hours spent on NCPAP were less in the B group as well as the days of hospitalization, while in a study carried out in the neonatal unit of the Medical City in Baghdad showed longer hospital stay in NCPAP survivors compared to ventilated infant although higher mortality was noted in the ventilated group after CPAP failure.[23]

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