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The Effect of Surfactant Accompanied by Ventolin on the Respiratory Distress Syndrome in Premature Newborns: A Clinical Trial Study

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Abstract

Background

The respiratory distress syndrome (RDS) is one of the most common respiratory disorders in premature newborns. The aim of this study was to determine the effect of surfactant accompanied by Ventolin on the RDS in premature newborns.

Materials and Methods

The study was a double-blind randomized controlled trial that was conducted on 80 premature newborns with RDS in Imam Reza Hospital of Kermanshah, Iran, in 2018. The eligible newborns, using a random number table, were divided into two groups of surfactant with Ventolin as intervention group (n=40) and surfactant with normal saline as control group (n=40). The data collection tool was a checklist, including the demographic characteristics (gender, birth weight, gestational age, etc.) and clinical variables (length of hospitalization, pneumothorax, need of Continuous Positive Airway Pressure (CPAP), mechanical ventilation, tachypnea duration, RDS score, etc.). Data were analyzed using SPSS software (version 24.0).

Results

The results of the study showed that the two groups of intervention and control have significant statistical difference in terms of RDS score, tachypnea duration**,** duration of taking oxygen, start time of oral feeding, length of hospitalization, partial pressures of oxygen (PaO2), partial pressure of carbon dioxide (PaCO2), need of mechanical ventilation and pneumothorax, respiratory rate, heart rate, oxygen saturation and FIO2 after intervention (P<0.05). However, there were no significant statistical differences between the two groups in terms of need of CPAP and outcome (P>0.05).

Conclusion

The results of this study showed that administration surfactant accompanied by Ventolin can lead to decrease in RDS score, improve the respiration status, reduce start time of oral feeding and also reduce length of hospitalization.

Key Words: Premature, Respiratory distress syndrome, Surfactant, Newborn, Ventolin.

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1- INTRODUCTION

According to the most recent report by the World Health Organization (WHO), 15 million premature neonates are born annually worldwide (1-4). Respiratory distress syndrome (RDS), known as hyaline membrane disease, is a common and severe disease which frequently occurs in premature infants (5, 6). The RDS is the most common cause for admission of newborns in the Neonatal Intensive Care Unit (NICU) and caused by deficiency of surfactants, is one of the main causes of disease complications and death in preterm infants. The most common symptoms of this syndrome that can be mentioned include tachypnea, poor feeding, cyanosis, nasal flaring grunting, intercostal retraction and reduction of respiratory sounds in pulmonary auscultation (7-9).

Generally, the RDS incidence rate is 6-7% in newborns, however, the syndrome has an inverse and strong relationship with the gestational age, so that the highest incidence rate is seen in premature infants (10-12). The studies have shown that the RDS incidence rate for infants under 28, 32-36 and over 36 weeks is 60-80, 15-30 and 5%, respectively. Unfortunately, despite the proposed treatment and supportive measures, the disease is responsible for 50% of all neonatal deaths (13). Reducing the production and secretion of surfactants is the primary cause of the RDS. So that, 65% of severe premature infants require moderate mechanical ventilation and 50% need treatment for surfactants (14, 15).

Pulmonary surfactant deficiency leads to extensive atelectasis, pulmonary residual capacity reduction and ventilation-perfusion ratio inequality, which, in the absence of proper treatment, death occurs due to inappropriate gas exchange, pneumothorax, emphysema, pulmonary hemorrhage and bleeding in the ventricles of the brain (16-18). In the last period of pregnancy, the pulmonary fluid volume is somewhat greater than the intrapulmonary volume. The process of delivery plays an important role at the start of clearance of fluid from the lungs and preparation for air respiration, but the main mechanism for clearing the lungs of fluid is active transport of sodium mediated via Na^+/K^+-Adenosine triphosphatase (ATPase) channel (19, 20). Several factors can contribute to increasing the absorption of pulmonary fluid. Evidence suggests that high levels of catecholamines at birth may be important in accelerating the clearance of fluid from the lungs (21, 22). Studies have also shown that β2 receptor agonists increase the activity of sodium channel through the induction of the mechanism of cyclic adenosine monophosphate-protein kinase A (CAMP-PKA) (23).

It has also been shown that β2 receptor agonists increase sodium channel activity by inducing the mechanism of CAMP-PKA. Ventolin (as a β2 receptor agonist) is a sympathetic emulator with direct effect, which has β-adrenergic receptors stimulatory activity and selective activity in relation to β2 receptors. When administered as an inhaler it causes relaxation of bronchial smooth muscles and finally opens up the medium and large airways in the lungs (23-25).

A meta-analysis study of randomized controlled trials aimed to evaluate the effect of Ventolin (Salbutamol) in the treatment of acute respiratory distress syndrome (ARDS) has showed that treatment with Ventolin in the early course of ARDS is not effective in increasing the survival but significantly decreases the ventilator-free days and organ failure-free days (26). Although some studies have been conducted separately on the effect of surfactant and Ventolin in the treatment of RDS, based on our knowledge limited studies have been done about the effect of surfactant plus Ventolin in the treatment of premature newborns with RDS. Therefore, the present study aimed to evaluate the

efficacy of surfactant plus Ventolin in the treatment of premature newborns with RDS.

2- MATERIALS AND METHODS

2-1. Study Design and Subjects

This study was a double-blind randomized controlled trial (RCT) that was conducted on 80 premature newborns with RDS hospitalized in intensive care unit of Imam Reza Hospital of Kermanshah (Iran), a single sitting method from 1st of November 2018 to 31st of March 2019. The NICU section of Imam Reza Hospital has 22 beds. In this study, sampling was done in an available method. Then a randomization was done. To determine the sample size, Dehdashtian et al.'s study was used (20). Sample size was determined as follows:

$$\text{Sample size} = \frac{2(Z_{\alpha/2} + Z_{\beta})^2 P(1-P)}{(p_1 - p_2)^2}$$

Where, α=0.05, β=0.8, P1=0.7, P2=0.4 and P-value less than 0.05 was considered statistically significant. The diagnostic criteria for RDS included occurrence of respiratory distress after birth of premature infant and chest X-ray positive findings (air reduction, reticulogranular pattern, and air bronchogram) (27). Inclusion criteria included premature infant with RDS (28 to 34 weeks), birth weight ≥ 1000 gr and negative blood culture; exclusion criteria included the absence of radiographic findings for RDS, birth asphyxia, birth trauma, congenital anomalies, severe metabolic acidosis and heart rate > 180 per minute.

2-2. Data Collection

In the present study, the data collection tool was a checklist, including the demographic and clinical variables such as sex, birth weight, gestational age, type of delivery, Apgar score, length of hospitalization (days), mother's asthma history, mother's diabetes history, start time of oral feeding (day), pneumothorax, need for continuous positive airway pressure (CPAP), partial pressure of oxygen (PaO2), partial pressure of carbon dioxide (PaCO2), need for mechanical ventilation, duration of taking oxygen, tachypnea duration, infant outcome (death or live) as well as measurement of main clinical parameters including respiratory distress score, respiratory rate, heart rate, oxygen saturation (%), fraction of inspired oxygen (FIO2) at 4 different time periods. RDS score was determined according to the **Table.1** (28).

2-3. Intervention

Before the study began, the research objectives were explained for the infant's parents and informed consent was obtained from them. Then, eligible newborns were divided into two groups using a random number table (intervention group, n=40; control group, n=40). Then, for the intervention group surfactant with Ventolin and for the control group surfactant with normal saline were administered as a single dose. In other words, for the intervention group, Ventolin (product of India) was given at a dose of 0.2 mg/kg plus surfactant and also for the control group, surfactant was administered plus 0.5 ml/kg normal saline.

It should be noted that in both groups under study the surfactant (product of pharmaceutical company Chiesi, Italy) was administered within 2 h after birth, the initial dose was 2.5 ml/kg and the subsequent doses were 1.5 ml/kg. Then, the variables studied in both groups were evaluated and compared in 4 different times which include: before intervention, 30 min, 1 h and 4 h after intervention. In this study, the pneumothorax variable was evaluated by chest X-ray and the PAO2 and PACO2 variables were evaluated by Arterial Blood Gases (ABG) **Figure 1**.

Table-1: RDS Scores (28).

Clinical Symptoms	0	1	2
Number of respirations per minute	Less than 60	60 to 80	More than 80
Cyanosis	Not in ambient air	Not under the hood	Yes, under the hood
Intercostal retraction	No	Moderate	Severe
Respiratory sounds	Good	Reduced	Not heard
Granting	No	Only with Stethoscope	Without Stethoscope

RDS: respiratory distress syndrome.

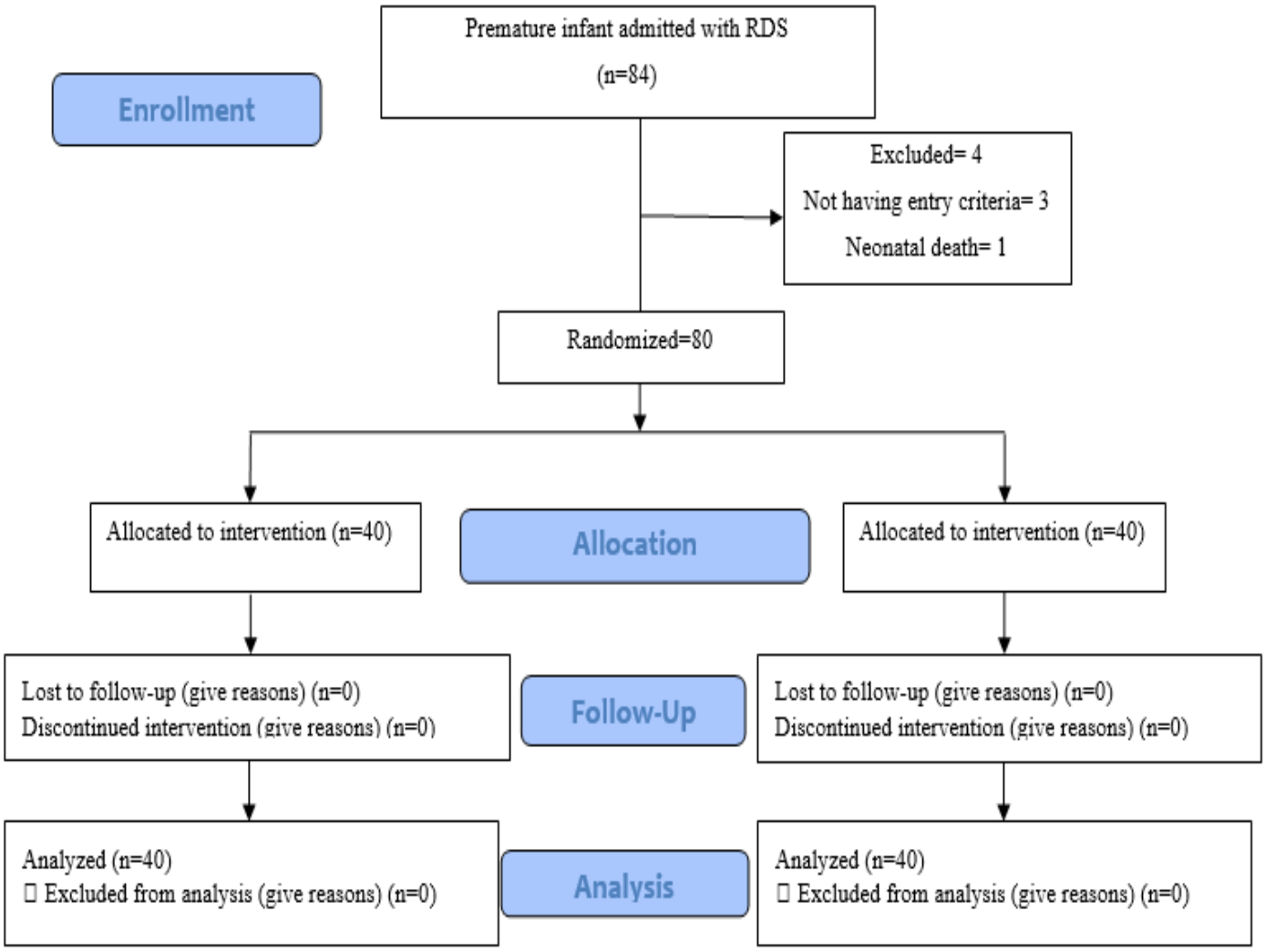

Fig.1: Consort flowchart.

2-4. Statistical Analyses

In descriptive analysis, mean (standard deviation [SD]), and number (%) were used for quantitative and qualitative variables, respectively. In analytical analysis, the independent-samples T-test (existence of normal distribution), Mann–Whitney U test (lack of normal distribution) and Chi-square test were employed to compare the quantitative and qualitative variables in two groups. Finally, Repeated Measure ANOVA test was used to compare the means of quantitative variables at different time periods in the two groups of intervention and control. It should be noted that the data were analyzed using SPSS software (version 24.0), and P-value <0.05 was considered as significant level.

2-5. Ethical Considerations

The protocol study was conducted according to the principles expressed in the Declaration of Helsinki and was approved by the Deputy of Research and Ethics Committee of Kermanshah University of Medical Sciences (ID-number: IR.KUMS.REC.1397.940). Additionally, this clinical trial study was registered in Iranian Registry of Clinical Trials (registration ID: IRCT20151220025619N5). Before the intervention, after the explanation of the goals and method of the study, informed consent was obtained from the parents of the newborns.

3- RESULTS

The study was conducted on 80 premature newborns with RDS hospitalized in intensive care unit of Imam Reza Hospital of Kermanshah, Iran. These newborns were randomly divided into the two groups of intervention (n=40) and control (n=40). **Table.2** shows baseline characteristics in two groups of intervention and control. For example, the mean birth weight of newborns in the intervention and control groups were 1473 ±368.70 and 1521 ±419.57 gr, respectively. The number of girls and boys in intervention group was 15 (37.5%) vs. 25 (62.5%), and also for control was 18 (45%) vs. 22 (55%), respectively. Generally, as can be seen, there were no significant statistical differences between the two groups under study in terms of baseline variables of birth weight, gender, gestational age, 1 and 5 minute Apgar score, type of delivery, mother's asthma history and mother's diabetes history (P>0.05). This lack of significant statistical difference between the two groups can be a can be a reason for the accurate occurrence of the randomization process (**Table.2)**.

Table-2: Determination and comparison of baseline variables in two groups of Intervention and Control.

Quantitative Variables		Group	Number	Mean	SD	P-value
*Birth Weight (gram)		Intervention	40	1473	368.70	0.584
		Control	40	1521	419.57	
**Gestational Age		Intervention	40	32.35	2.27	0.950
		Control	40	32.30	2.37	
**1 minute Apgar Score		Intervention	40	6.60	0.87	0.141
		Control	40	5.95	1.30	
**5 minute Apgar Score		Intervention	40	7.82	0.75	0.06
		Control	40	7.47	1.01	
Qualitative Variables		Intervention Group		Control Group		P-value
		Number	%	Number	%	
Sex of Infant	Girl	15	37.50	18	45	0.496
	Boy	25	62.50	22	55	

Type of Delivery	NVD	9	22.50	12	30	0.446
	CS	31	77.50	28	70	
Mother's History of Diabetes	Yes	9	22.50	4	10	0.130
	No	31	77.50	36	90	
Mother's History of Asthma	Yes	0	0	0	0	1
	No	40	100	40	100	
*: Independent-Samples T-Test. **: Mann–Whitney U Test. NVD: Normal Vaginal Delivery. CS: Caesarean Section; SD: Standard Deviation.						

After the intervention, the results of the independent-samples T-test and Mann–Whitney U test showed that there are significant statistical differences between the two groups of intervention and control in terms of clinical variables of tachypnea duration**,** duration of taking oxygen, start time of oral feeding, length of hospitalization, PAO2, PACO2; so that the mean of variables of tachypnea duration**,** duration of taking oxygen, start time of oral feeding, length of hospitalization and PACO2 in the intervention group were lower than the control group. Also, the mean of PAO2 in the intervention group was higher than the control group after intervention. In addition, the results of Chi-square test indicated that there are significant statistical differences between the two groups under study in terms of need for mechanical ventilation and pneumothorax (P<0.05) **(Table.3)**. Also, **Figures 2-6** show the variations of these variables at different time periods.

Table-3: Determination and comparison of clinical variables under study in two groups of Intervention and Control.

Quantitative Variables		Group	N	Mean	SD	P-value
*Tachypnea Duration (hours)		Intervention	40	52.07	16.64	<0.001
		Control	40	76.47	17.17	
*Duration of Taking Oxygen (hours)		Intervention	40	53.65	18.39	<0.001
		Control	40	82.22	16.22	
*Start Time of Oral Feeding (days)		Intervention	40	2.56	1.007	<0.001
		Control	40	4.21	1.45	
**Length of Hospitalization (days)		Intervention	40	11.20	3.01	<0.001
		Control	40	17.10	5.01	
**PAO2		Intervention	40	99.67	24.87	<0.001
		Control	40	66.16	10.86	
**PACO2		Intervention	40	40.83	9.87	<0.001
		Control	40	55.09	8.94	
Qualitative Variables		Intervention Group		Control Group		P-value
		Number	%	Number	%	
Need for Mechanical Ventilation	Yes	1	2.50	8	20	0.013
	No	39	97.50	32	80	
Need of CPAP	Yes	40	100	39	97.50	0.314
	No	0	0	1	2.50	
Pneumothorax	Yes	0	0	4	10	0.040
	No	40	100	36	90	
Outcome	Death	2	5	3	7.50	0.644
	Live	38	95	37	92.50	
*: Mann–Whitney U Test. **: Independent-Samples T-Test. PAO2: Partial pressure of oxygen; PACO2: Partial Pressure of Carbon Dioxide; CPAP: Continuous positive airway pressure; SD: Standard Deviation.						

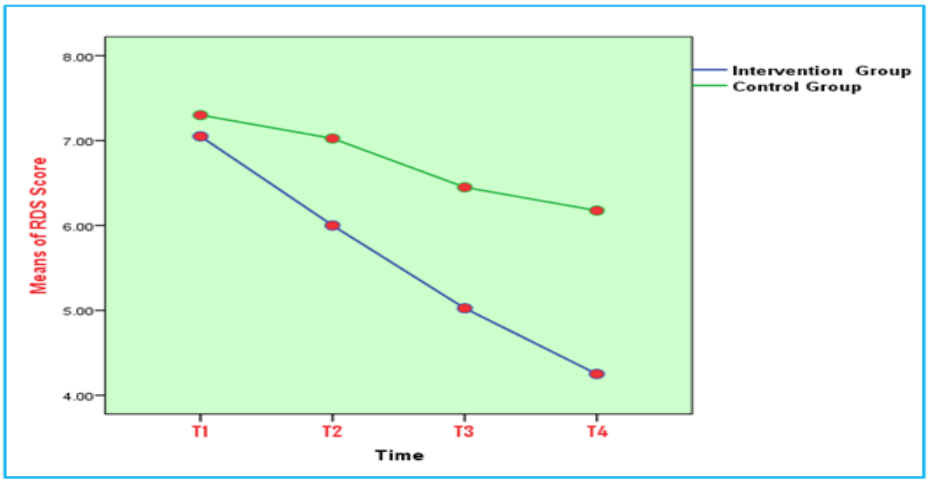

Fig.2: The Means of RDS Score in two groups of Intervention and Control at different time periods (Repeated Measure ANOVA test).

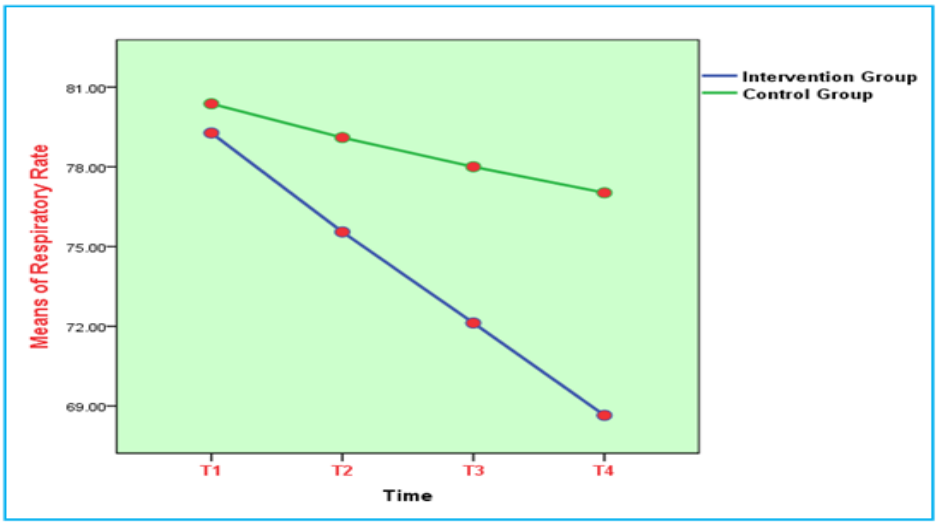

Fig.3: The Means of Respiratory Rate in two groups of Intervention and Control at different time periods (Repeated Measure ANOVA test).

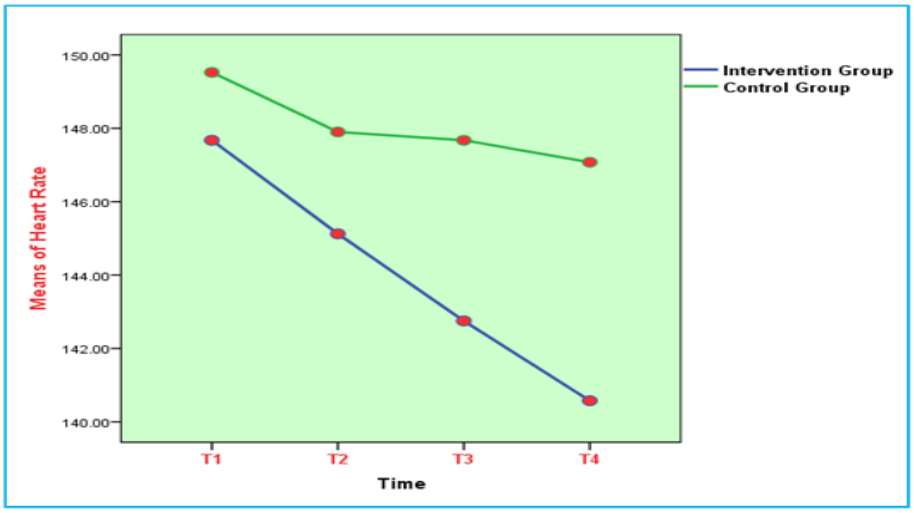

Fig.4: The Means of Heart Rate in two groups of Intervention and Control at different time periods (Repeated Measure ANOVA test).

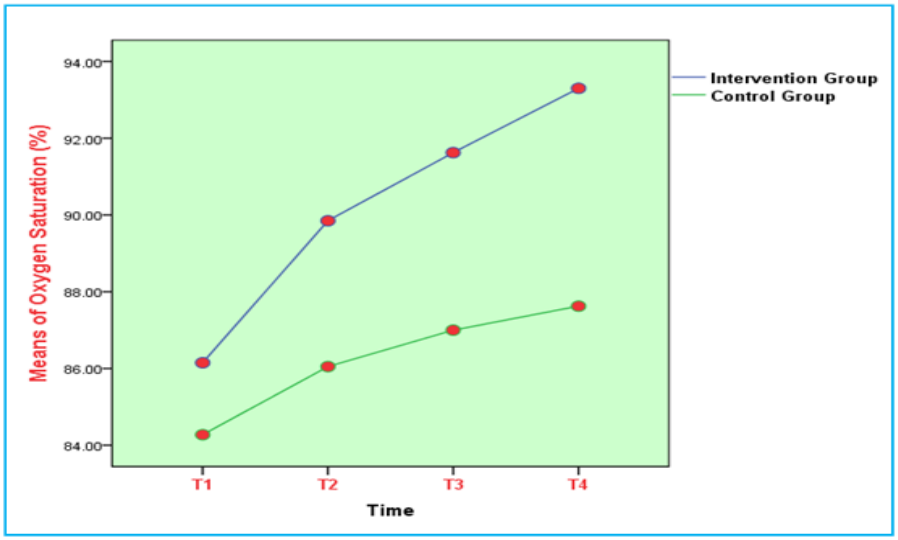

Fig.5: The Means of Oxygen Saturation (%) in two groups of Intervention and Control at different time periods (Repeated Measure ANOVA test).

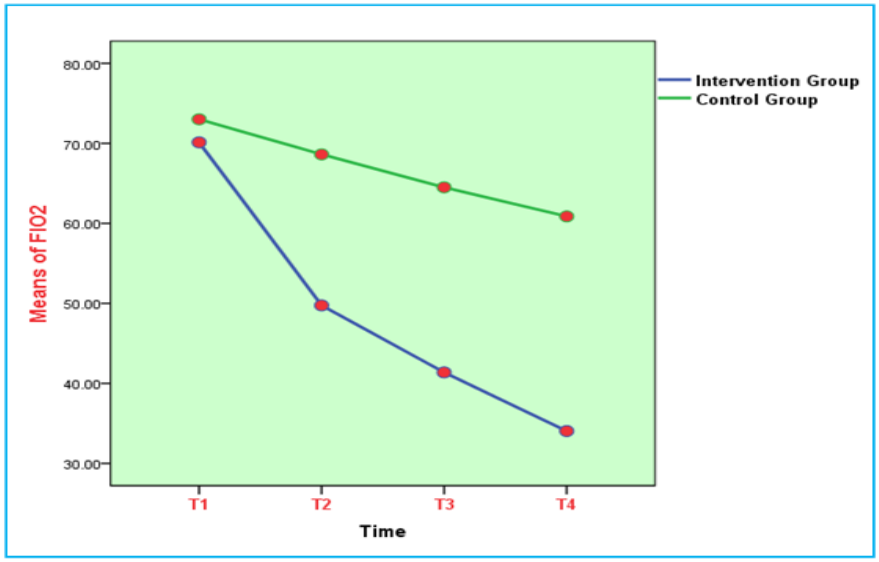

Fig.6: The Means of FIO2in two groups of Intervention and Control at different time periods (Repeated Measure ANOVA test).

In the present study, Repeated Measure ANOVA test was used to compare the means of quantitative variables between the two groups of intervention and control at different time periods. The results of the test showed that there are significant statistical differences between the two groups of intervention and control in terms of variables of RDS score, respiratory rate, heart rate, oxygen saturation (%), Fraction of inspired oxygen (FIO2) at 4 different time periods ($P<0.05$); so that, the mean of variables of RDS score, respiratory rate, heart rate, and FIO2 in the intervention group were lower than the control group at 4 different time periods. Also, the mean of oxygen saturation (%) in the intervention group was higher than the control group at 4 different time periods (**Table.4**).

Table-4: Determination and comparison of the means of primary outcomes in two groups of Intervention and Control at different time periods (Repeated Measure ANOVA Test).

**RDS Score	Group	Number	Mean	SD	P-value *
Time 1: Before intervention	Intervention	40	7.05	0.81	
	Control	40	7.30	0.56	
Time 2: 30 minutes after intervention	Intervention	40	6.00	0.93	
	Control	40	7.02	0.70	<0.001
Time 3:1 hour after intervention	Intervention	40	5.02	1.02	
	Control	40	6.45	0.75	
Time 4: 4 hours after intervention	Intervention	40	4.25	1.03	
	Control	40	6.17	1.01	
Respiratory Rate	Group	Number	Mean	S.D	P-value *
Time 1 : Before intervention	Intervention	40	79.27	6.42	
	Control	40	80.37	6.007	
Time 2: 30 minutes after intervention	Intervention	40	75.55	6.03	
	Control	40	79.10	6.41	<0.001
Time 3: 1 hour after intervention	Intervention	40	72.12	5.44	
	Control	40	78.00	6.79	
Time 4: 4 hours after intervention	Intervention	40	68.65	5.49	
	Control	40	77.02	6.54	
Heart Rate	Group	Number	Mean	SD	P-value *
Time 1: Before intervention	Intervention	40	147.67	4.42	
	Control	40	149.52	3.93	
Time 2: 30 minutes after intervention	Intervention	40	145.12	3.86	
	Control	40	147.90	3.74	<0.001
Time 3: 1 hour after intervention	Intervention	40	142.75	3.46	
	Control	40	147.67	4.36	
Time 4: 4 hours after intervention	Intervention	40	140.57	4.21	
	Control	40	147.07	4.53	
Oxygen Saturation (%)	Group	Number	Mean	SD	P-value *
Time 1: Before intervention	Intervention	40	86.15	5.34	
	Control	40	84.27	5.54	
Time 2: 30 minutes after intervention	Intervention	40	89.85	4.19	
	Control	40	86.05	5.94	<0.001
Time 3:1 hour after intervention	Intervention	40	91.62	4.60	
	Control	40	87.00	5.18	
Time 4: 4 hours after intervention	Intervention	40	93.30	4.14	
	Control	40	87.62	5.37	
***FIO2	Group	Number	Mean	S.D	P-value *
Time 1: Before intervention	Intervention	40	70.12	10.47	
	Control	40	73.00	12.90	
Time 2: 30 minutes after intervention	Intervention	40	49.75	14.76	
	Control	40	68.62	15.19	<0.001
Time 3:1 hour after intervention	Intervention	40	41.37	13.82	
	Control	40	64.50	14.67	
Time 4: 4 hours after intervention	Intervention	40	34.05	14.17	
	Control	40	60.37	15.92	

*P-value: Significant level for Interaction Group and Time (Repeated Measure ANOVA Test).
RDS Score: The respiratory distress syndrome score
FIO2: Fraction of inspired oxygen.

4- DISCUSSION

The aim of this study was to determine the effect of surfactant accompanied by Ventolin on the RDS in premature newborns. The results of the study demonstrated that the two groups of intervention and control have significant statistical difference in terms of tachypnea

duration**,** duration of taking oxygen, start time of oral feeding, length of hospitalization, PAO2, PACO2, need for mechanical ventilation and pneumothorax after intervention (P<0.05). Also, the results of Repeated Measure ANOVA test revealed that there are significant statistical differences between the two groups of intervention and control in terms of RDS score, respiratory rate, heart rate, oxygen saturation (%), and FIO2 at 4 different time periods after intervention (P<0.05). These findings were consistent with the findings of some studies conducted in this field. For example, the study by Dehdashtian et al. indicated that intervention group (surfactant with Ventolin) had a lower degree of nasal continuous positive airway pressure (NCPAP) failure and the need for mechanical ventilation than the control group (surfactant with normal saline).

Also, the same study showed that the duration of NCPAP, mechanical ventilation, oxygen therapy and duration of hospitalization were shorter in interventional group than the control group (20). The study by Mussavi et al. that aimed to evaluate the effect of salbutamol in improvement of respiratory distress in neonates showed significantly decreased RDS score in salbutamol group compared to placebo group (from 5.6 at the start to 1.7 at the end of study vs. 5.6 to 3.9, respectively).

In the same study, the duration of CPAP was significantly lower in salbutamol group compared to placebo group after intervention (1.6 ± 0.77 vs. 3.3 ± 0.98) (29). Another study by Armangil and colleagues to evaluate the effects and side effects of salbutamol in treatment of tachypnea of the newborn (TTN) indicated significant reduction in the need for respiratory support level, oxygen requirement and respiratory rate in salbutamol group vs. control group. Also, the levels of PCO2 and PO2 in the Salbutamol group were better than the control group (30). A meta-analysis study of randomized controlled trials aimed to evaluate the effect of Ventolin in the treatment of acute respiratory distress syndrome (ARDS) has demonstrated that treatment with Ventolin significantly decreased the ventilator-free days and organ failure-free days and also, the duration of taking oxygen in the group receiving Ventolin was significantly shorter than the control group (26).

In another study by Kim et al. to investigate the effect of inhalational salbutamol therapy on improvement of clinical symptoms in transient tachypnea of the newborn (TTN), the results showed that the duration of supplemental oxygen therapy, duration of empiric antibiotic treatment and duration of tachypnea were significantly shorter in the salbutamol group versus control group (31). Also, the research by Didem Armangil et al. in Ankara, Turkey (2011) revealed significant positive changes in terms of respiratory rate, clinical score of transient tachypnea of the newborn (TTN), fraction of inspired oxygen, and level of respiratory support in the salbutamol group compared with normal saline. Finally, the study concluded that inhaled salbutamol treatment can be effective on clinical and laboratory findings of TTN (26).

In a another similar research by Kamrani et al. aimed to determine the effects of surfactant on the mortality and complications of RDS in neonates, the results showed that the use of surfactant in preterm infants with RDS significantly decreased mortality and also the incidence of pneumothorax, septicemia and pulmonary hemorrhage (32). In contrast, there were some other studies that were not in line with the study results and they have not shown the effectiveness of Ventolin on DRS. For example, the systematic review by Luca Moresco and colleagues that aimed to determine the

effect of salbutamol (Ventolin) on transient tachypnea in the newborn with gestational age ≥ 34 weeks showed that salbutamol has no significant effect on the duration of hospitalization and tachypnea, and finally concluded that there is insufficient evidence to prove the efficacy and safety of salbutamol in the treatment of tachypnea of the newborn, which may be due to low sample size and low methodological quality of studies conducted in this field (33). The study of Kim et al. demonstrated that the duration of hospitalization in the infants who received salbutamol has no significant difference with the control group (31).

Also, the clinical trial study of Dehdashtian et al. did not show significant difference between two intervention (surfactant with Ventolin) and control groups (surfactant with normal saline) in terms of mortality and morbidity such as Patent ductus arteriosus (PDA) and pneumothorax (20). A similar research by Mussavi et al. showed that there is no significant statistical difference in terms of PACO2 between two groups of salbutamol and placebo (29). The inconsistency of these studies with our study results may be due to differences in sample size, different outcomes under study, different control and intervention groups and also methodological differences.

5- CONCLUSION

The results of this study suggests that administration of surfactant accompanied by Ventolin can significantly decrease RDS score, duration of tachypnea, duration of taking oxygen, length of hospitalization, need for mechanical ventilation, respiratory rate, heart rate, FIO2, PACO2 and risk of pneumothorax. Also, this combination can significantly increase PAO2 and oxygen saturation. Therefore, given the high incidence of DRS in premature infants and its complications, the administration of surfactant accompanied by Ventolin is recommended in these infants.

6- CONFLICT OF INTEREST: None.

7- ACKNOWLEDGEMENTS

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