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Evaluation of Vitamin D in Preterm Neonates and Effects of its Supplementation in Preterm Neonates with Respiratory Distress Syndrome

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ABSTRACT

Background: Prematurity and related problems, especially respiratory distress syndrome, are one of the main challenges for neonatal medicine. Many studies have shown the relationship between lung development and vitamin D.

Objective: To investigate Vitamin D status and to evaluate the effect of vitamin D supplement as adjuvant therapy in the management of respiratory distress syndrome (RDS) in preterm infants.

Patients and Methods: This study included 90 preterm neonates chosen from those at NICU of Minya General Hospital and Al-Azhar University, Assiut, Egypt. The cases were divided into two main groups; a group with RDS (case group 66 cases) and a group without RDS (control group =24 cases). The group with RDS was further subdivided into three subgroups (subgroup I received just traditional therapy and the subgroup II received traditional therapy plus vitamin D 400 IU/day, while subgroup III received traditional therapy plus vitamin D 800 IU/day).

Results: The RDS group had lower neonatal and maternal vitamin D concentrations than the group without RDS. We found a strong positive correlation between neonatal and maternal vitamin D levels on the day of delivery. The subgroups supplemented with vitamin D had a significant improvement in all ABG parameters, lower Downs score, less hospital stay, less morbidity than the subgroup without vitamin D supplementation.

Conclusion: Administration of vitamin D as adjuvant therapy in cases of RDS was associated with a significant decrease in severity, rate of complications, and duration of hospital stay in the subgroup received 800 IU/Day compared to the subgroup received 400 IU/Day.

Keywords: Vitamin D, Preterm neonates, Respiratory distress syndrome

INTRODUCTION

Prematurity is the most important risk factor predisposing to neonatal RDS. Preterm birth continues to be an important public health problem globally and is a leading cause of perinatal death and disability worldwide [(1)].

Preterm neonates can have many complications such as respiratory distress syndrome (RDS), intraventricular hemorrhage, necrotizing enterocolitis, bronchopulmonary dysplasia, sepsis, persistent ductus arteriosus, and retinopathy [(2)].

Even in late preterm newborns whose gestational ages are between 34-36 weeks, infection, hyperbilirubinemia, feeding difficulties are more common than in term babies. **Kalyoncu *et al.*** [(3)] have reported 2.3% mortality and 11 times more respiratory distress syndrome (RDS) compared to term babies.

Respiratory distress syndrome (RDS) is the commonest cause of respiratory failure during the first days after birth. In addition to prematurity, other factors contributing to the development of RDS such as maternal diabetes, cesarean delivery without preceding labor, fetal asphyxia, and being the second twins [(4)].

Vitamin D is a steroid hormone, responsible mainly for the maintenance and regulation of calcium levels in the body as well as the development of a healthy skeleton [(5)].

Serum levels of 25-hydroxyvitamin D are considered the best circulating biomarker of vitamin D metabolic status and reflect contributions from all sources of vitamin D i.e., diet and sun exposure [(6)].

Maternal and neonatal vitamin D deficiency is alarmingly high in Arabs and significantly associated with each other. One study showed that almost 85% of Arab pregnant women and 88% of their neonates had vitamin D deficiency or insufficiency [(7)].

As pregnancy is a time of tremendous growth and physiological changes in the developing fetus, vitamin D and its metabolites could affect the genetic signaling of the developing fetus and could minimize the risk of certain adverse outcomes through a not fully understood mechanism [(8)].

Because the placental transfer of vitamin D is the major source of vitamin D to the developing fetus, this does mean that a mother deficient in vitamin D is equal to a fetus deficient in vitamin D. with increased risk of various maternal and fetal adverse effects, including increased risk of gestational diabetes mellitus, preeclampsia, small for gestational age, and other tissue- specific conditions [(9)]. Antenatal

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vitamin D supplementation increases neonatal 25(OH) D levels**.** Vitamin D deficiency may also have a role in several diseases involving the respiratory system [(10)].

It has also been shown that vitamin D deficiency in utero and early life alters lung development, decreases lung volume, and impairs lung function [(11)]. Also, People who have low vitamin D levels may have a higher chance of getting a respiratory infection [(5)].

This study aimed to investigate Vitamin D status and to evaluate the effect of vitamin D supplementation as adjuvant therapy in the management of respiratory distress syndrome (RDS) in preterm infants.

PATIENTS AND METHODS

This study is a Prospective Case-Control study that was conducted on 90 preterm neonates, their ages ranged between 30 weeks to 36 weeks' gestation using the New Ballard Score. They were chosen from those at the neonatal intensive care unit (NICU) and neonatal wards of the Pediatric Department of Minya General Hospital and Al-Azhar University Assiut, Egypt between February 2020 and August 2020.

Ethical considerations:

The study was approved by the ethical committee of the Pediatric Department of Minya General Hospital and Al-Azhar University, Assiut. The parents of all participants had signed written informed consent.

Study flow chart:

The cases were divided according to the presence or absence of RDS, using the Downs Respiratory Distress score system **into two main groups**; a group with RDS **(case group = 66 cases)** and a group without RDS **(control group = 24 cases)**. The group with respiratory distress was further subdivided by serial computerized randomization into three subgroups according to the assigned management.

Subgroup I includes 22 preterm newborns diagnosed with respiratory distress syndrome was given the traditional therapy of RDS (O_2 therapy, assisted ventilation, and surfactant therapy according to the clinical guidelines).

Subgroup II includes 22 preterm newborns diagnosed with respiratory distress syndrome was given vitamin D in the low ideal dose (400 IU/Day) in addition to the traditional therapy of RDS.

Subgroup III includes 22 preterm newborns diagnosed with respiratory distress syndrome was given vitamin D in the high ideal dose (800 IU/Day) in addition to the traditional therapy of RDS.

Once the diagnosis of RDS was established, we immediately started with vitamin D therapy for subgroup II&III as indicated and continued the same protocol till RDS was resolved.

Supplementation with vitamin D was continued after discharge from the NICU and at home for all the babies incorporated in the study including the control group and the first subgroup without supplementation.

Inclusion criteria: Preterm newborns admitted to NICU for routine care of prematurity and those who had respiratory distress syndrome admitted to the NICU. The ages of those infants ranged between 30 weeks and 36 weeks gestation.

Exclusion criteria: Full-term neonates, preterm less than 30 weeks, preterm babies with apparent congenital anomalies, apparent chromosomal anomalies, preterm with neonatal sepsis, newborn with hypoxia, infant of a diabetic mother, newborns with feeding intolerance.

All preterm neonates were subjected to the following:

A) Complete history taking:

- **Maternal history:** Maternal age, mode of delivery (vaginal or cesarean section), twins, complications during any previous pregnancy**.**
- **Neonatal history:** Gestational age, Sex.

B) Clinical examination:

- **General examination:** Vital signs, weight, head circumference, abdominal circumference, APGAR score at 1 and 5 minutes, and assessment of gestational age (GA) using the New Ballard score.
- **Systemic examination:** Respiratory examination Using Downs score, Cardiovascular, Abdominal, and Neurological examination.

C) Laboratory investigation which includes:

- Routine laboratory investigations.
- Serum (maternal and neonatal) 25-hydroxyvitamin D by ELISA technique.

All these investigations were done on the 1st day of life.

D) Follow Up of the three RDS subgroups:

- **On days 1, 3, and 7:** The three RDS subgroups were evaluated by Down score, A.B.G, Hospital stay duration, Morbidity, and mortality.
- **On day 21 of life**: Blood samples were taken from the serum of infants of subgroup II and III again for measuring the serum 25 hydroxyvitamin D level by ELISA kits.

Statistical analysis

Data were collected, coded, revised, and entered the Statistical Package for Social Science (IBM SPSS) version 20. The data were presented as numbers and percentages for the qualitative data, mean, standard deviations, and ranges for the quantitative data with parametric distribution, and median with interquartile range (IQR) for the quantitative data with the non-parametric distribution. Chi-square test was used in the comparison between two groups with qualitative data and Fisher exact test was used instead of the Chi-square test when the expected count in any cell found less than 5. Independent t-test was used in the comparison between two groups with quantitative data and the parametric distribution and Mann-Whitney test

was used in the comparison between two groups with quantitative data and non-parametric distribution. The comparison between more than two groups with quantitative data and parametric distribution was done by using the One-Way Analysis of Variance (ANOVA) test and the Kruskal-Wallis test was used in the comparison between more than two groups with quantitative data and non-parametric distribution. Spearman correlation coefficients were used to assess the significant relation between two quantitative parameters in the same group. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the following: P > 0.05: Non-significant (NS). P < 0.05: Significant (S). P < 0.01: Highly significant (HS).

RESULTS

Table (1): Comparison between the two participated groups as regards demographic data.

Total cases (n = 90)							
		Control group (n=24)		RDS group (n=66)		Chi square test/ Independent t test	
		No	%	No	%	X^2/t*	P-value
Sex	Female	10	41.7%	32	48.5%	0.329	0.566
	Male	14	58.3%	34	51.5%		
Delivery mode	CS	8	33.3%	40	60.6%	5.26	0.022
	VD	16	66.7%	26	39.4%		
Twins Pregnancy	No	20	83.3%	34	51.5%	7.424	0.006
	Yes	4	16.7%	32	48.5%		
Birth weight	Mean ± SD	2225.17 ± 143.86		2005.15 ± 366.38		2.854*	0.005
Head circumference	Mean ± SD	30.95 ± 1.77		29.75 ± 1.59		3.080*	0.003

This table shows that there was a statistically significant increase in cesarean section, twins' gestation in the RDS group but there was a statistically significant increase in weight and Head circumference in the control group.

Table (2): Comparison between the two groups as regards maternal age & gestational age, Apgar score at 1 and 5 minutes, and maternal vitamin D.

Total cases (n = 90)						
	Control group (n=24)		RDS group (n=66)		Independent t test	
	Mean	SD	Mean	SD	t	P-value
Maternal age	27.67	3.67	27.45	4.56	0.205	0.838
Gestational age	32.50	1.79	32.81	1.96	0.696	0.488
Apgar score 1 m	7.17	1.61	5.36	1.35	5.309	0.001
Apgar score 5m	7.92	1.14	7.00	1.24	3.166	0.002
Maternal vitamin D	26.50	8.01	17.61	4.07	6.932	0.001

This table shows that there was no statistically significant difference in maternal age and gestational age regarding studied groups. There was a statistically significant increase in Apgar score at 1 and 5 minutes in the control group**.** There was a statistically significant increase in maternal vitamin D in the control group.

Table (3): Comparison between both groups as regards neonatal Vitamin D after delivery

Total cases (n =90)							
		Control group (n=24)		RDS group (n=66)		Chi-square test/ Independent t test	
		No	%	No	%	X^2/t*	P-value
Neonatal vitamin D after delivery	Less than 10	0	0.0%	10	15.2%	10.970	0.012
	From 10 to 20	10	41.7%	36	54.5%		
	From 20 to 30	6	25.0%	14	21.2%		
	More than 30	8	33.3%	6	9.1%		
	Mean ±SD	25.50 ± 8.89		18.18 ± 7.52		3.885	0.001

Vitamin D levels assay: Vitamin D sever deficiency: 25(OH) D < 10 ng/ml. Vitamin D deficiency: 25(OH) D (10 – 20) ng/ml. Vitamin D insufficiency: 25(OH) D (20 – 30) ng/ml. Vitamin D sufficiency: 25(OH) D (30 – 100) ng/ml. **This table shows:** That there was a statistically significant increase in neonatal vitamin D after delivery in the control group. The most common level of vitamin D in the studied groups after delivery is (10 - 20 ng/ml) which is vitamin D deficiency**.**

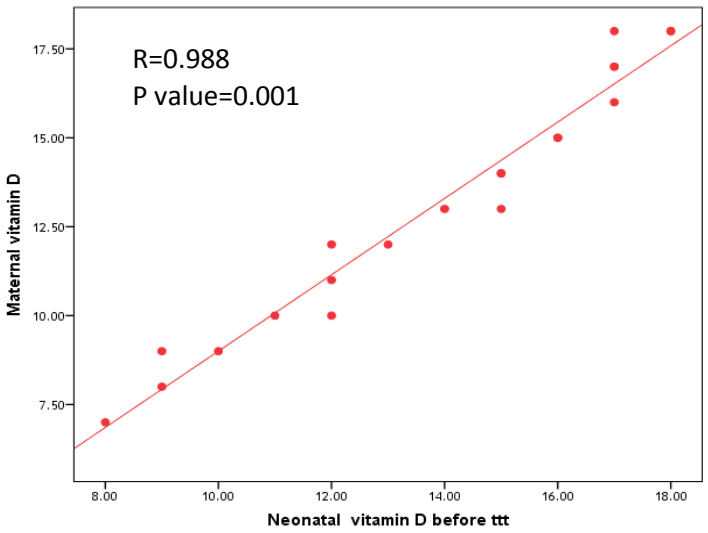

Figure (1): Positive correlation between Neonatal vitamin D and maternal vitamin D after delivery in all the studied groups. There was a strong positive correlation between neonatal vitamin D and maternal vitamin D after delivery in all studied groups.

Table (4): Comparison between RDS groups (group I, II, and III) as regards demographic data

		Group I (n=22)		Group II (n=22)		Group III (n=22)		Chi-square test/ One-way ANOVA	
		No	%	No	%	No	%	X^2/f*	P-value
Sex	Female	10	45.5%	10	45.5%	12	54.5%	0.485	0.785
	Male	12	54.5%	12	54.5%	10	45.5%		
Delivery mode	CS	14	63.6%	12	54.5%	14	63.6%	0.508	0.776
	VD	8	36.4%	10	45.5%	8	36.4%		
Twins pregnancy	No	12	54.5%	10	45.5%	12	54.5%	0.485	0.785
	Yes	10	45.5%	12	54.5%	10	45.5%		
Birth weight	Mean ± SD	1931.82	354.07	2036.36	345.62	2047.27	402.68	0.659	0.521
Head circumference	Mean ± SD	29.79	1.46	29.82	1.67	29.64	1.70	0.081	0.922

Group I: Traditional therapy of RDS.
Group II: Vitamin D in the low ideal dose (400 IU/Day).
Group III: Vitamin D in the high ideal dose (800 IU/Day).
This table shows that there was no statistically significant difference in demographic data regarding RDS groups (group I, II, and group III).

Table (5): Comparison between RDS groups (group I, II, and group III) as regards maternal age and gestational age, Apgar score.

	Group I (n=22)		Group II (n=22)		Group III (n=22)		One-way ANOVA	
	Mean	SD	Mean	SD	Mean	SD	F	P-value
Maternal age	27.36	3.58	27.64	4.30	27.36	5.74	0.025	0.975
Gestational age	32.81	2.08	32.81	2.08	32.81	1.78	0.158	0.924
Apgar score 1 m	5.36	1.26	5.45	1.47	5.27	1.39	0.096	0.908
Apgar score 5 m	6.91	1.02	7.18	1.30	6.91	1.41	0.347	0.708

Group I: Traditional therapy of RDS.
Group II: Vitamin D in the low ideal dose (400 IU/Day).
Group III: Vitamin D in the high ideal dose (800 IU/Day).
This table shows that there was no statistically significant difference in maternal age and gestational age regarding RDS groups (group I, II, and group III). There was no statistically significant difference between RDS groups (group I, II, and group III) as regards the Apgar score.

Table (6): Comparison between RDS groups (groups I, II, and III) as regards maternal vitamin D and neonatal vitamin D before and after treatment.

	Group I (n=22)		Group II (n=22)		Group III (n=22)		One-way ANOVA	
	Mean	SD	Mean	SD	Mean	SD	F	P-value
Maternal vitamin D	17.55	3.39	17.36	4.35	17.91	4.55	0.100	0.905
Neonatal Vitamin D After delivery (before treatment)	17.73	3.62	18.64	3.05	18.18	4.20	0.078	0.925
Neonatal Vitamin D after treatment	--	--	46.09	6.78	61.45	10.33	34.001*	0.001
Parried t-test								
Vitamin D before VS after treatment	--		0.001		0.001		--	

*Independents t-test

Group I: Traditional therapy of RDS.
Group II: Vitamin D in the low ideal dose (400 IU/Day).
Group III: Vitamin D in the high ideal dose (800 IU/Day).

This table showed: There was a statistically significant increase in group II as regard vitamin D level after treatment as compared to before treatment. There was a statistically significant increase in group III as regard vitamin D level after treatment as compared to before treatment. There was a statistically significant increase as regard vitamin D level after treatment in group III as compared to group II.

Table (7): Comparison between RDS groups (group I, II, and group III) as regards Complication**.**

Complications	Group I (n=22)		Group II (n=22)		Group III (n=22)		Chi-square test	
	No	%	No	%	No	%	X^2/f*	P-value
No	13	59.1%	18	81.8%	20	90.9%	6.729	0.034
Yes	9	40.9%	4	18.2%	2	9.1%		
BPD	1	11.1%	0	0.0%	0	0.0%	7.743	0.458
pulmonary hemorrhage	1	11.1%	0	0.0%	1	50%		
ventilator acquired pneumonia	3	33.3%	1	25.0%	0	0.0%		
Pneumothorax	2	22.2%	2	50.0%	1	50%		
Sepsis	2	22.2%	1	25.0%	0	0.0%		

Group I: Traditional therapy of RDS.
Group II: Vitamin D in the low ideal dose (400 IU/Day).
Group III: Vitamin D in the high ideal dose (800 IU/Day).

This table showed there was a statistically significant decrease in the complications between the three studied groups as group III is lower than group II and group II is lower than group I. These complications were in the form of bronchopulmonary dysplasia, pneumothorax, pulmonary hemorrhage, ventilator acquired pneumonia and sepsis.

DISCUSSION

In the present study, as regarding the demographic data of preterm babies with RDS **(case group)** and those without RDS **(control group),** It showed no significant differences between the two groups as regarding the maternal age (P-value = 0.838) and the gestational age (P-value = 0.488).

The same results were reached by **Loughrey and Rimm** [(12)] found no significant difference in infants of RDS when compared to infants without RDS, in gestational age more than 30 weeks and this might be the same cause of our results as a range of our gestational age was 30-36 weeks.

While this comes in disagreement with **Qari *et al.*** [(13)] as this study was conducted on 395 RDS patients that showed that the incidence of RDS increases with decreasing gestational age and infants born below 30 weeks gestation are at the greatest risk for RDS.

In the present study, there was no significant difference between the RDS group **(case group)** and the group without RDS **(control group)** regarding their

sex (P-value = 0.566). However, the percentage of male patients (51.5%) is high as compared to the female ones (48.5%) in the RDS group.

This comes in agreement with **Rao *et al.*** [14] who found that male sex independently increases the risk for RDS in preterm neonates as he studied 200 preterm newborns with RDS, 128 of them (64%) were males and 72 (36%) were females.

This can be explained by the theory that male fetuses have lower numbers of cuboidal cells that change into type II alveolar cells, dihydrotestosterone synthesized by male delays surfactant production. Consequently, males become distressed more easily [15].

In the present study, as regarding the birth weight and head circumference, there was a statistically significant decrease in birth weight (P-value = 0.005) and Head circumference (P-value = 0.003) in preterm babies with RDS.

This comes in agreement with **Gomella and Cunningham** [16] reported that hyaline membrane disease occurs in 50% of infants with birth weight between 501 and 1500g.

Also In the present study, we found that the preterm group with RDS had significantly decreased APGAR at 1 and 5 minutes (P-value = 0.001, P-value = 0.002), increased percentage of twins pregnancy (P-value = 0.006), an increased percentage of cesarean section (P-value = 0.022), than the preterm group without RDS.

This comes in agreement with **Heinzmann *et al.*** [17] as they suggested that the cesarean section is an additional risk factor of neonatal respiratory distress. Also, comes in agreement with **Anadkat *et al.*** [18] as he studied 895 preterm newborns diagnosed with RDS, 57.2% were delivered by Caesarean section and they defined the cesarean section as an independent predictor of RDS. This finding could be explained on the basis that normal labor enhances neonatal lung adaptation by inducing a surge of catecholamine in the fetus which stimulates the absorption of fetal lung fluid, inhibit secretion of the fetal lung fluid, and increase the release of surfactant [19].

Although this disagrees with **Rao *et al.*** [14] as their study was conducted on 200 babies 124 (62%) were delivered by normal vaginal delivery and 76 (38%) were delivered by cesarean section. 66.7% of newborns (82 out of 124) born by normal vaginal route developed severe respiratory distress compared to 47% of the newborns (36 out of 76) by cesarean section.

In the present study, as regarding maternal 25(OH)D and neonatal 25(OH) D concentration, there was a statistically significant decrease in maternal 25(OH)D (P-value = 0.001) and neonatal 25(OH)D (P-value = 0.001), in the preterm group with RDS.

We found a significant positive correlation between neonatal vitamin D level and maternal vitamin D at delivery (P-value = 0.001) in all studied groups.

This comes in agreement with **Pilz *et al.*** [20] have demonstrated that there is a strong correlation between the 25(OH) Vitamin D level of the mother and fetus.

This also comes in agreement with **Yu *et al.*** [21] found that there is a correlation between 25(OH)Vitamin D deficiency in the mother and preterm birth.

In our study, the mean value of neonatal 25(OH)D level in preterm group with RDS was (18.18 ± 7.52 ng/ml) and in healthy preterm neonates was (25.50 ± 8.89 ng/ml).

This comes in agreement with **Reffat *et al.*** [22], measurement of the vitamin D level in preterm neonates with RDS (9.52 ± 2.48ng/mL) versus healthy preterm infants (31.25±1.23ng/mL) showed that preterm infants with RDS had severe deficiency ($p<0.001$).

This also comes in agreement with **Hegazy *et al.*** [23], who found that preterm neonates with RDS had significantly lower mean serum 25(OH)D concentration than those without RDS. The group with RDS and low 25(OH)D concentration had prolonged hospitalization duration than those without.

In the present study, we found that a high percentage of the studied preterm neonates with RDS had either vitamin D deficiency or insufficiency as 10 of the studied patients (15.2%) had serum 25-OHD level at the 1st day of life; below 10 ng/ml (Vitamin D severe deficiency), 36 of the patients (54.5%) had serum 25-OHD level between 10 – 20 ng/ml (Vitamin D deficiency) and 14 of the patients (21.2%) had serum 25-OHD level between 20 – 30 ng/ml (vitamin D insufficiency) and 6 of the patients (9.1%) had serum 25-OHD level more than 30 ng/ml (normal vitamin D level).

This comes in agreement with **Ataseven *et al.*** [24], 152 neonates of 29-35 weeks gestation were investigated. In this study, 64% of neonates had a severe deficiency in 25-OH D (less than 10 ng/ml), 33% had moderate deficiency (10-20ng/mL) and there was a mild deficiency in 3% of neonates (20-30 ng/mL). RDS was more common (28%) in cases of severe vitamin D deficiency compared with neonates with moderate to mild deficiency (14%).

Now, we will discuss the comparison between the three RDS subgroups (I, II, III).

- **Subgroup I: Traditional therapy of RDS.**
- **Subgroup II: Vitamin D in the low ideal dose (400 IU/Day).**
- **Subgroup III: Vitamin D in the high ideal dose (800 IU/Day).**

In the present study as regarding the demographic data of the RDS subgroups (I, II, and III), there was no significant difference between them as regard sex (P-value = 0.785), the birth weight (P-value = 0.521), and the head circumference (P-value = 0.922).

This comes in agreement with **Mathur *et al.* [25]** who found no significant difference regarding the birth weight and head circumference between the 50 preterm newborns included in their study.

In the present study, there were no statistically significant differences between the studied RDS subgroups (I, II, and III) regarding twins' pregnancy and the mode of delivery. However, we denote that cesarean section delivery (60.6%) is more common than the normal vaginal delivery (39.4%) in RDS groups but does not reach statistical value.

There was no statistically significant difference between all the studied RDS subgroups (I, II, and III) as regard APGAR score at 1 and 5 minutes, maternal and gestational age. This comes in agreement with **Boskabadi *et al.* [26]** as the study was conducted on 160 preterm newborns with no significant difference between the studied groups as regarding the gestational age.

In the present study, the mean value of serum 25-OHD level at the 1st day of life in group I was 17.73 ± 7.62 ng/ml, group II was 18.64 ± 8.05, and group III was 18.18 ± 7.20 ng/ml, which shows no significant difference between the three studied groups (P-Value = 0.925).

Regarding the given dose in the present study as Vitamin D_3 was given to group II is 400 IU/Day & group III is 800 IU/Day. This comes in agreement with the American Academy of Pediatrics which recommended that the dose of Vitamin D was 400 IU/Day [27]. While The European Society for Pediatric Gastroenterology, Hepatology and Nutrition has recommended higher intakes of vitamin D of 800–1000 IU/day for preterm infants, Although this vitamin D intake is likely safe, no data are available for very low-birth weight infants and especially infants with birth weight <1000 g to assess the safety of providing these vitamin D intakes [28].

In the present study, we concluded that there was a statistically significant improvement in 25-OHD level in group II supplemented with 400 IU/day after treatment with a mean value 46.09 ± 6.78 ng/ml as compared to before treatment with a mean value 18.64 ± 8.05 ng/ml (P-value = 0.001), and in the group, III supplemented with 800 IU/day after treatment with mean value 61.45 ± 10.33 ng/ml as compared to before treatment with mean value 18.18 ± 7.20 ng/ml (P-value =0.001).

There was also a statistically significant improvement in 25(OH)D level in group III as compared to group II after treatment (P = 0 .001).

This agreed with the work of **Anderson- Berry *et al.* [29],** who found that a daily dose of 800 IU of vitamin D for preterm infants significantly improves vitamin D concentration at 4 weeks than a dose of 400 IU.

In the present study, we found as regarding the complication which includes (Broncho-Pulmonary dysplasia, pneumothorax, Ventilator - acquired pneumonia, pulmonary hemorrhage, and sepsis): There was a statistically significant decrease in the complication between the three studied subgroups as group III (9.1**%**) is lower than group II (18.2 **%**) and group II is lower than group I (40.9**%)** (P-value = 0.034). We found no studies with or against our findings in decreasing the complication between our three studied subgroups with our recommended vitamin D doses intake.

However, we found some studies which prove that the severity of BPD was inversely related to 25 (OH) D levels. A study conducted by **Cetinkaya *et al.* [30]** investigated the association between vitamin D deficiency and BPD in premature infants (gestational age ≤32 weeks) who were admitted to the NICU with a diagnosis of RDS. In this survey, 25(OH) D levels were significantly lower in both infants with BPD and their mothers ($p<0.05$).

CONCLUSIONS

1. 25 hydroxy-vitamin D levels were found deficient in most preterm babies especially those who developed RDS.
2. Administration of vitamin D as adjuvant therapy in cases of RDS was associated with a significant decrease in severity, rate of complications, and duration of hospital stay in the subgroup received 800 IU/Day compared to the subgroup received 400 IU/Day.

RECOMMENDATIONS

1. Evaluation of serum 25-hydroxy Vitamin D level may be recommended as a routine investigation in cases of RDS.
2. Vitamin D supplementation may be used as adjuvant therapy in the treatment of RDS.
3.

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