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The relationship between Vitamin A and Vitamin E levels and neonatal morbidities

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Abstract. – OBJECTIVE: In the neonatal period, diseases such as respiratory distress syndrome, necrotizing enterocolitis, bronchopulmonary dysplasia, retinopathy of prematurity, intraventricular hemorrhage, patent ductus arteriosus hypoxic-ischemic encephalopathy, and hyperbilirubinemia are frequently seen, despite being differently affected by the gestational age. This study aims to examine the relationship between morbidities in the neonatal period and serum vitamin A and vitamin E levels.

PATIENTS AND METHODS: In this prospective cohort study, patients who were treated and followed up in the Neonatal Intensive Care Unit between August 2020 and September 2021 were evaluated.

RESULTS: 381 patients, 202 male (53%) and 179 female (47%), were included in the study. The mean birth weight was 2642.13±835.91 g (minimum 480 g, maximum 4285 g) and the mean gestational week was 35.3±3.8 (minimum 24 weeks, maximum 42 weeks). The weight of 332 patients (87.2%) was above 1500 g in whom there was a significant increase in respiratory distress, hypoxic-ischemic encephalopathy, and hyperbilirubinemia correlated with a decrease in the vitamin E levels (p=0.001, 0.02, and 0.001, respectively). In infants over 32 weeks of age, there was a significant increase in respiratory distress, hypoxic-ischemic encephalopathy, and hyperbilirubinemia correlated with a decrease in the vitamin E levels (p=0.001, 0.02, and 0.001, respectively). No significant relationship was found between vitamin A levels and neonatal morbidities regardless of the birth weight or gestational age.

CONCLUSIONS: We believe that our study may provide convenience to pediatricians and neonatologists in terms of the relationship between vitamin A and E levels and neonatal morbidities in neonates.

Key Words:
Hyperbilirubinemia, Hypoxic-ischemic encephalopathy, Newborn, Respiratory distress syndrome, Vitamin A, Vitamin E.

Introduction

Morbidities that occur in the neonatal period differ depending on the maturity of the patients. In premature infants, diseases such as respiratory distress syndrome (RDS), necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), intraventricular hemorrhage (IVH), and patent ductus arteriosus (PDA) are seen more frequently, while in term infants, respiratory distress (RD), hypoxic-ischemic encephalopathy (HIE) and hyperbilirubinemia (HB) are more common.

Vitamin A is a fat-soluble micronutrient that has important roles in the development and maturation of various tissues and organs, such as pulmonary alveolar epithelial cells, retinal development, epithelium, bone, and immune system[1]. Premature infants born with inadequate body stores of vitamin A and especially extremely low birth weight (ELBW) infants need vitamin A for the development of the lungs and the retina. Low vitamin A levels in these infants may increase the risk of RDS and may cause adverse pulmonary outcomes, leading to chronic pulmonary diseases[1,2]. In addition, vitamin A deficiency may reduce both cellular and humoral immunity in the intestinal mucosa and increase intestinal permeability[3]. Vitamin A deficiency may significantly increase neonatal morbidity and mortality[1].

Vitamin E is one of the fat-soluble vitamins that cannot be synthesized by the body and must be obtained mainly from fats[4]. Vitamin E has a very important role in fetal lung development[4]. Since the normal development of the lungs is interrupted due to preterm birth, vitamin E deficiency may be more common in premature infants and infants with low birth weight[4]. Preterm infants who are not breastfed have lower concentrations of vitamin E after birth[5]. Colostrum and

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transitional milk have higher vitamin E content compared to formula and TPN[6]. Vitamin E protects neonates from diseases related to oxidative stress such as hemolytic disease and BPD[7,8].

The aim of this study is to evaluate the relationship between vitamin A and vitamin E levels and neonatal morbidities in term and preterm neonates.

Patients and Methods

Patients

In this prospective cohort study, patients who were treated and followed up in the Neonatal Intensive Care Unit (NICU) between August 2020 and September 2021 were evaluated.

Inclusion Criteria

Patients who were born at 24 weeks of gestation or later and hospitalized at NICU were included.

Exclusion Criteria

Patients born before 24 weeks of gestation and patients with major congenital anomalies, dysmorphic symptoms suggestive of chromosomal abnormality, a prenatal diagnosis of chromosomal abnormality, or orcyanotic congenital heart disease were excluded.

Ethics Committee and Approval of the Study

The study was conducted at Dicle University Training and Research Hospital between August 2020 and September 2021. The study protocol was approved by the institutional Ethics Committee of Dicle University (16.07.2020/306). The study was conducted according to the approved protocols following all recommendations and regulations of the Local Ethics Committee and in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

Diagnosis and Definitions

Neonatal specialists with clinical experience performed the check-ups of the neonates. Clinical findings were recorded prospectively in real-time into the electronic medical record system of the hospital. The patients with neonatal diseases were admitted to the Department of Neonatology for treatment.

The respiratory distress, jaundice, HIE, RDS, BPD, NEC, and IVH status of the patients were assessed and recorded during the follow-up. Hyperbilirubinemia was defined as neonatal jaundice following the elevation of indirect bilirubin levels requiring phototherapy[9]. Respiratory distress was used to express a variety of conditions requiring respiratory support, including oxygen therapy, mechanical ventilation, continuous positive airway pressure (CPAP), Nasal SIMV (synchronized intermittent mandatory ventilation), and nasal catheter[10]. Respiratory distress syndrome was considered in cases of classic RD signs and the exclusion of other causes of respiratory failure. The diagnosis of RDS was radiologically confirmed by the presence of reduced lung volume, reticulogranular pattern, and air bronchograms[10]. Retinopathy of prematurity is a disease of abnormal retinal neovascularization, which is predominantly seen in very preterm infants and is generally caused by systemic inflammation[11]. Patent ductus arteriosus was defined as the ductus arteriosus that continue to remain open after birth[10]. The most widely applied definition of BPD is the requirement for supplemental oxygen at 36 weeks of corrected gestational age[12]. It was also defined as the presence of clinical evidence of BPD with oxygen therapy on the 28th day of life[12]. Necrotizing enterocolitis was diagnosed clinically and radiographically using the modified Bell's staging criteria[13].

Quantitation of Vitamin A and Vitamin E levels

At the time of admission to the hospital, blood samples were collected from peripheral veins into anticoagulant tubes and then centrifuged at 4°C for 15 minutes. The obtained plasma supernatants were stored at –20°C until analysis. The levels of vitamin A and E in the plasma samples were determined in duplicates by high-performance liquid chromatography (HPLC) according to the manufacturer's instructions (Shimadzu LC-20A, Immuchrom GmbH).

The patients were divided into low or sufficient vitamin A or vitamin E levels as follows: a vitamin A level of <200 μg/L was considered as a low vitamin A level and a vitamin A level of ≥200 μg/L was considered as a normal vitamin A level. According to the World Health Organization (WHO), a serum vitamin A level of <200 μg/L was considered as the diagnostic criterion for vitamin A deficiency in children aged 6-70 months and older[14]. Likewise, a vitamin E level of <500 μg/dL was considered as a low vitamin E level and a vitamin E level of ≥500 μg/dL was consid-

ered as a normal vitamin E level[15]. In most studies, this diagnostic criterion has also been used in neonates. For vitamin E deficiency, a serum vitamin E level of <500 µg/L was considered as the diagnostic criterion for low vitamin E level[4,7].

Statistical Analysis

The distribution of data was analyzed using the Kolmogorov-Smirnov test. Normally distributed data were expressed as mean±standard deviation, and continuous variables were compared using the Student's *t*-test; while for the comparison of data that did not follow a normal distribution, the Mann-Whitney U test was used. Quantitative data were expressed as numbers (%). A *p*-value of < 0.05 was considered statistically significant. All data were analyzed using the IBM Statistical Package for the Social Sciences (SPSS).

Results

The study included 381 patients. Of these patients, 53% (202) were male and 47% (179) were female. The mean birth weight was 2642.13±835.91 g (minimum 480 g, maximum 4285 g) and the mean gestational week was 35.3±3.8 (minimum 24 weeks, maximum 42 weeks). Forty-nine patients (12.8%) were 1500 g and below, and 332 patients (87.2%) were above 1500 g in weight. No significant relationship was found between RDS, NEC, BPD, ROP, and IVH morbidities and the vitamin E levels in infants weighing 1500 g and below, while in infants above 1500 g, a statistically significant increase was found in the frequency of RD, HIE, and HB, and this increase was correlated with a decrease in the vitamin E levels (p=0.001, 0.02, and 0.001, respectively) (Table I). In terms of gestational age, 69 patients (18.1%) were 32 weeks or below and 312 (89.9%) were over 33 weeks. No significant relationship was found between RD, HIE, and HB morbidities and the vitamin E levels in infants 32 weeks and below, while in infants over 32 weeks of gestational age, a statistically significant increase was found in the frequency of RD, HIE, and HB with a decrease in the vitamin E levels (p=0.001, 0.02 and 0.001, respectively) (Table II).

Our data show no significant relationship between vitamin A levels and neonatal morbidities regardless of the birth weight or gestational week (Table I and Table II).

Table I. Evaluation of the relationship between birth weight and neonatal morbidities.

			Vitamin A level (µg/L)			Vitamin E level (µg/L)		
Morbidity	**Status**	**N**	**Mean ± SD**	**Rank**	***p***	**Mean ± SD**	**Rank**	***p***
≤ 1500 g								
RDS	With	42	171 ± 86	25.4	0.62	590.7 ± 557.2	24.4	0.47
	Without	7	161 ± 10	22.5		602.2 ± 334.3	28.5	
NEC	With	10	199 ± 87	30.4	0.17	841.1 ± 840.2	30.5	0.16
	Without	39	162 ± 87	23.6		528.5 ± 406.2	23.5	
BPD	With	12	198 ± 93	30.2	0.14	854.4 ± 828.4	29.8	0.17
	Without	37	160 ± 85	23.3		507.3 ± 363.6	23.4	
ROP	With	14	185 ± 77	28.1	0.32	654.0 ± 755.1	23.9	0.74
	Without	35	163 ± 91	23.7		567.7 ± 417	25.4	
IVH	With	7	245 ± 12	36.7	0.01	1043.4 ± 1005	33.5	0.09
	Without	42	157 ± 75	23.1		517.1 ± 372.1	23.5	
PDA	With	9	164 ± 53	25.8	0.84	640.7 ± 928.8	20.3	0.28
	Without	40	171 ± 94	24.8		581.4 ± 407.4	26.1	
> 1500 g								
RD	With	42	174 ± 31.9	142.5	0.08	259 ± 185.8	91.6	**< 0.001**
	Without	290	158 ± 19.2	169.9		556.8 ± 466.1	177.3	
HIE	With	28	178 ± 7.2	215.2	0.29	321.5 ± 246.4	113.3	**0.002**
	Without	304	158 ± 2.2	162.1		537.5 ± 461.7	171.3	
HB	With	125	149 ± 9	170.6	0.54	728.8 ± 530.5	223.2	**< 0.001**

*BPD: Bronchopulmonary dysplasia, HIE: Hhypoxic-ischemic encephalopathy, HB: Hyperbilirubinemia, IVH: Intraventricular hemorrhage, NEC: Necrotizing enterocolitis, PDA: Patent ductus arteriosus, ROP: Retinopathy of prematurity, RD: Respiratory distress, RDS: Respiratory distress syndrome.

Table II. Evaluation of the relationship between gestational age and neonatal morbidities.

Morbidity	Status	N	Vitamin A level (µg/L)			Vitamin E level (µg/L)		
			Mean ± SD	Rank	p	Mean ± SD	Rank	p
≤32 week								
RDS	With	53	172 ± 84	37.4	0.06	549.5 ± 516	34.9	0.99
	Without	16	133 ± 75	26.7		469.7 ± 268	35.1	
NEC	With	12	189 ± 84	42.2	0.17	750.3 ± 793	33.5	0.19
	Without	57	157 ± 83	33.4		484.8 ± 363.1	41.7	
BPD	With	12	198 ± 93	44.7	0.06	854.4 ± 828.4	44.8	0.06
	Without	57	155 ± 80	32.9		462.9 ± 325.5	32.9	
ROP	With	14	185 ± 77	41.8	0.14	654 ± 755.1	36.4	0.76
	Without	55	157 ± 84	33.2		499.7 ± 368.2	34.6	
IVH	With	7	245 ± 22	52.7	0.09	1043 ± 379.9	48.9	0.18
	Without	62	154 ± 73	33.1		473.2 ± 336.1	33.4	
PDA	With	9	164 ± 53	38.1	0.21	640.7 ± 928.8	35.5	0.28
	Without	60	163 ± 87	34.5		514.6 ± 367.6	31.3	
> 32 week								
RD	With	42	174 ± 31	134.6	0.09	259.8 ± 185.8	85.4	**< 0.001**
	Without	270	159 ± 19	159.9		569.8 ± 476.8	167.5	
HIE	With	28	178 ± 72	151.9	0.005	321.5 ± 246.4	105.4	**0.002**
	Without	284	159 ± 22	202.2		548.5 ± 472.2	161.5	
HB	With	124	149 ± 91	160.2	0.55	732.4 ± 531.1	122.1	**< 0.001**
	Without	188	169 ± 27	154.1		393.4 ± 348.9	208.7	

*BPD: Bronchopulmonary dysplasia, HIE: Hhypoxic-ischemic encephalopathy, HB: Hyperbilirubinemia, IVH: Intraventricular hemorrhage, NEC: Necrotizing enterocolitis, PDA: Patent ductus arteriosus, ROP: Retinopathy of prematurity, RD: Respiratory distress, RDS: Respiratory distress syndrome.

Discussion

In this study, we examined the relationship between vitamin A and vitamin E levels and some neonatal morbidities. Fetuses cannot synthesize vitamin A and therefore depend primarily on the maternal placental source during the last trimester of pregnancy. Furthermore, the retinol-binding protein produced in the fetal liver in the last quarter of pregnancy plays a vital role in fetal vitamin A transport[14]. Premature infants have low levels of vitamin A since they cannot synthesize enough retinol-binding protein to transport vitamin A into the cells[14]. Vitamin A signals through retinoic acid receptors in the lung cells to synthesize pulmonary surfactant and help lung maturation and function[14]. Vitamin A deficiency is associated with many diseases such as nyctotyphlosis, xerophthalmia, keratomalacia, corneal ulcer, dysfunctions of the immune system, and respiratory tract infections[14]. In addition, vitamin A deficiency may decrease both cellular and humoral immunity in the intestinal mucosa, increasing intestinal permeability and leading to the conditions such as NEC[3]. It is thought that premature infants have vitamin A deficiency in their lungs at birth, and pulmonary vitamin A requirements are relatively high during the first weeks of life, especially in those with chronic lung disease[2]. In some studies[1,16-21], vitamin A deficiency was found to be as high as 42-82% in neonates. Tao et al[14] found the prevalence of vitamin A deficiency in late preterm infants to be 37.5%. In other studies[22,23], the incidence of neonatal vitamin A deficiency was found to be 60.1% in regions where vitamin A deficiency is not common. It was also suggested that biological levels of neonatal vitamin A at birth may be much lower than the vitamin A levels in adults[22, 23]. Liu et al[1] reported very low vitamin A levels among completely healthy term infants. There was no significant difference in vitamin A levels and the clinical findings at the postnatal 6th month between the groups of patients with vitamin A deficiency who received and who did not receive vitamin A supplementation[1]. It is reported that diet, geography, culture, age, preterm birth, and infectious diseases are important factors affecting vitamin A levels[15]. Bezerra et al[21] reported that the high prevalence of vitamin A deficiency was not a determinant in infection of preterm neonates. Kiatchoosakun et al[16] suggested that vitamin A supplementation might reduce the intubation time and oxygen support and shorten the length of hospital stay. However,

Uberos et al[24] reported no difference in the duration of oxygen therapy between the patients receiving vitamin A supplementation and control groups[24]. Tao et al[14] reported that a vitamin A level of <0.7 μmol/L in late preterm infants was not an independent risk factor for hospitalization, oxygen support, or RDS[14]. Although it was thought that vitamin A might increase surfactant synthesis, it might not have a significant effect on late preterm and term infants, who are relatively mature compared to early preterm infants[14]. Therefore, it has been suggested that applying the current diagnostic criteria for vitamin A deficiency, which are for older children, may not be valid for neonates with vitamin A deficiency[1]. Our results confirm those of Tao et al[14] and Uberos et al[24] but contradict those of Kiatchoosakun et al[16]. Our study also shows that there is no correlation between vitamin A levels and preterm morbidities such as ROP, NEC, IVH, and term morbidities such as RD, HIE, and HB. Therefore, our study supports the idea that the relationship between vitamin A levels and neonatal morbidities might have been previously overestimated.

Very low birth weight (VLBW) infants are at risk for vitamin A and vitamin E deficiencies due to inadequate intake and low storage of these vitamins. These deficiencies are more common in VLBW infants because they have a higher requirement for vitamin A and E than term infants[25]. Wu et al[26] reported that the mean serum concentration of α-tocopherol isoform of vitamin E was significantly lower in infants born at 28-34 gestational weeks than infants born at 38-42 weeks despite similar total vitamin E and total lipid ratios[26]. Kositamongkol et al[27] reported unexpected vitamin E deficiency in infants with VLBW, despite a high-dose vitamin E supplementation. Kaempf et al[28] reported that the vitamin E levels of the patients with vitamin E deficiency in the postnatal period returned to normal in the postnatal 6th week without any supplementation[28]. Jain et al[29] reported no relationship between maternal vitamin E levels and fetal vitamin E levels and neonatal birth weight[29]. In contrast, School et al[30] reported a positive relationship between maternal and neonatal plasma vitamin E concentrations and fetal birth weight. It is not clear whether the administration of specific vitamin E isoforms reduces the development of BPD and pulmonary morbidity in pregnant women at risk for preterm labor or in preterm infants at risk soon after birth[5]. In our study, no relationship was found between the vitamin E levels and neonatal morbidities such as RDS, BPD, NEC, and IVH in VLBW infants and premature infants born at 32 weeks or before. However, we found a statistically significant difference between the vitamin E levels and neonatal morbidities, such as RD, HB, and HIE in infants over 32 weeks of age and over 1500 g. It is plausible to argue that the antioxidant property of vitamin E protects erythrocytes from breakdown and thus bilirubin levels are kept within the normal range, and it protects against RD and HIE by preventing cell damage.

Limitations

Our study has some limitations. It was not designed to compare the clinical outcomes between infants with normal vitamin levels and infants with vitamin A or vitamin E deficiency. Some analyses are lacking due to the character of the study. The study, which was single centered with a limited number of patients, examined only the vitamin A and vitamin E levels of the patients at the time of admission. The results related to postnatal nutrition were not evaluated. In addition, during the study, the impact of conditions that affect the intestinal health of the patients, such as sepsis and NEC, on the subsequent vitamin levels were not evaluated. The mortality status of the patients was not evaluated and the patients who died were excluded from the study.

Conclusions

Although limited, our study found no relationship between neonatal morbidity and vitamin A levels of term and preterm infants. Likewise, we found no relationship between the vitamin E levels and neonatal morbidities in very low birth weight infants and premature infants born at 32 weeks or before. However, we found a statistically significant difference between the vitamin E levels and neonatal morbidities in infants over 32 weeks of age and over 1500 g. We believe that our study may provide convenience to pediatricians and neonatologists in terms of the relationship between vitamin A and E levels and neonatal morbidities in neonates.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Informed Consent

The informed consent for patients was taken before the beginning of the study.

Ethics Committee Approval

The study was approved by the Ethics Committee of Dicle University Faculty of Medicine (16.07.2020/306).

Authors' Contribution

All authors read and approved the final version of the manuscript. Medical Practices: Ibrahim Deger, Ilyas Yolbaş, Sabahattin Ertuğrul. Concept: Ibrahim Deger, Sabahattin Ertuğrul, Ibrahim Kaplan. Design: Ibrahim Deger, Sabahattin Ertuğrul, Sibel Tanrıverdi Yılmaz. Data Collection or Processing: Ibrahim Deger, Sabahattin Ertuğrul, Zuhal Koç Özbey. Analysis or Interpretation: Ibrahim Deger, Ibrahim Kaplan, Ilyas Yolbaş. Literature Search: Ibrahim Deger, Sabahattin Ertuğrul, Ibrahim Kaplan. Writing: Ibrahim Deger, Sabahattin Ertuğrul.

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