

## Original paper

# The association of oxidative stress of neonatal hyperbilirubinemia and vitamin E supplementation

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## Abstract

**Aim of the study:** Jaundice in newborns is a sign of skin and sclera pigmentation. Hyperbilirubinemia and these phenomena do, however, have a relationship. According to many clinical studies, elevated blood bilirubin and low vitamin E (VE) levels in newborns are associated. The aim of the study was to investigate the association of oxidative stress of neonatal hyperbilirubinemia in patients who underwent phototherapy with additional vitamin E supplementation (25 mg/kg/day over the course of three days) and patients without additional vitamin E.

**Material and methods:** A set of 100 neonatal indirect hyperbilirubinemia patients was enrolled at neonatal intensive care units (NICUs) of the pediatric departments at Al Azhar University Hospitals during the period from February 2021 to October 2022 after obtaining signed written informed consent of all neonates' parents with an explanation of the aim of study.

**Results:** Significant differences were found between the studied groups regarding serum bilirubin on the third day of admission ( $p = 0.039$ ). Patients who were treated with vitamin E had lower serum bilirubin on the third day of admission ( $8.25 \pm 3.41$ ) than the control group ( $11.66 \pm 3.22$ ). Also, among the VE group, serum bilirubin was significantly decreased on the third day of admission ( $8.25 \pm 3.41$ ) compared to zero days of admission ( $14.10 \pm 4.39$ ) ( $p = 0.041$ ).

**Conclusions:** Vitamin E supplementation has an important role in treatment of indirect hyperbilirubinemia in neonates. Early administration of vitamin E in preterm neonates resulted in a significant decrease of serum bilirubin and increased total antioxidant capacity. Vitamin E supplementation in full term decreased the duration of phototherapy.

**Key words:** hyperbilirubinemia, neonatal, oxidative stress, total antioxidant capacity, vitamin E.

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## Introduction

Neonatal hyperbilirubinemia is a common clinical problem encountered during the neonatal period, especially in the first week of life [1]. Between 8% and 11% of newborns experience hyperbilirubinemia. During the first week of life, when the total serum bilirubin (TSB) rises over the 95<sup>th</sup> percentile for age (high-risk zone) it is considered hyperbilirubinemia [2]. It is typical for idiopathic neonatal jaundice to occur in 60% to 80% of healthy newborns. A newborn's skin and sclera turn yellowish due to neonatal jaundice, which is caused by bilirubin [3].

A high serum level of free bilirubin may cause neurotoxicity, but mildly increased bilirubin concentrations are beneficial due to their protective antioxidant role in cells of membranes, while markedly decreased concentrations may also be harmful [4]. Although the amount of free bilirubin in the serum is reduced during the treatment of newborn hyperbilirubinemia, this may lessen the protective impact of bilirubin on the cell membrane, making the cell membrane vulnerable to damage and leading to cell apoptosis [5]. Overexpression of the BAX gene, which encourages apoptosis brought on by phototherapy, and the oxidative stress brought on by phototherapy may both be responsible for this damage [6].

Vitamin E plays a vital role in the natural metabolism of all cells and acts in conjunction with other nutrients and endogenous factors which could form a protective system against the destructive effects of reactive oxygen species [7]. Vitamin E is a crucial part of the cellular antioxidant defense system and participates in a few different antioxidant enzyme systems, including glutathione reductase, catalase, superoxide dismutase, glutathione peroxidase, and thioredoxin reductase [8].

By making red blood cells less susceptible to autoxidation processes, vitamin E appears to be able to stop physiological hemolysis and lower bilirubin formation [9]. Various clinical studies have revealed a connection between elevated blood bilirubin and lower vitamin E levels in newborns [10].

Oxidative stress occurs because of the imbalance between oxidant products and antioxidant systems [11]. Free radicals, or molecules with unpaired electrons, are molecules that are produced during metabolic redox reactions in response to hypoxic or hyperoxic conditions, ischemia-reperfusion, inflammation, immune response activation, mitochondrial dysfunction, and the Fenton reaction. They include reactive oxygen, nitric, carbonic, and sulfuric species [12].

Antioxidants can neutralize or eliminate free radicals, preventing tissue damage from oxidative stress, such as superoxide dismutase, catalase, glutathione peroxidase, vitamins C and E, minerals, and glutathione (GSH) [13]. Both term and preterm newborns produce more free radicals as a result of the birth's abrupt increase in oxygen concentration since they are unable to counterbalance this burden [14].

Due to the limited antioxidant capacity, which is mostly developed during the latter stages of pregnancy, as well as the immaturity of the antioxidant production system, premature babies are especially susceptible to the harm caused by oxidative stress [15].

Unconjugated idiopathic hyperbilirubinemia in newborns has been linked to the oxidative breakdown of red blood cells [16]. Hypoxia and acidosis in the fetus and infant have been linked to the mechanisms of oxidative damage. It has been demonstrated that children who develop idiopathic unconjugated hyperbilirubinemia have decreased levels of erythrocyte antioxidant enzymes due to the damaging effects of circulating oxidants that are not counterbalanced by appropriate antioxidant systems [12]. So, the aim of the study was to investigate the association of oxidative stress in neonatal hyperbilirubinemia and vitamin E supplementation. To this end, we investigated the association of oxidative stress in neonatal patients with hyperbilirubinemia who underwent phototherapy with additional vitamin E supplementation (25 mg/kg/day of over the course of three days) compared to patients without additional vitamin E.

## Material and methods

A set of 100 neonatal indirect hyperbilirubinemia patients was enrolled at neonatal intensive care units (NICUs) of the pediatric departments at Al Azhar University Hospitals during the period from February 2020 to October 2022 after obtaining signed written informed consent of all neonates' parents with an explanation of the aim of study. The protocol of this study was approved by the ethical committee of Al Azhar University, Faculty of Medicine (IRB ID: AZ-pedia2020-19). All studied neonates were divided into two groups:

- Group VE (cases) included 50 newborns with indirect hyperbilirubinemia who underwent phototherapy and were given 25 mg/kg/day of vitamin E over the course of three days commencing on the first day of admission;
- Group C (control) included 50 people receiving phototherapy without additional vitamin E who had indirect hyperbilirubinemia.

Inclusion criteria: neonatal indirect hyperbilirubinemia in both sexes. Exclusion criteria: neonatal direct hyperbilirubinemia in both sexes, signs of neonatal sepsis, and neonatal abnormalities (congenital, chromosomal...).

All neonates admitted to the NICU were subjected to:

- Full history taking including name, age, sex, mode of delivery, gestational age (weeks), nutrition status, factors that might lead to sepsis such as premature rupture of membranes, maternal fever, and vaginal discharge.
- Jaundice in a prior sibling, RH or ABO incompatibility, and a history of chronic hemolytic anemia in the family that manifested in the neonatal stage. Full clinical examination including vital data (heart rate, respiratory rate, and temperature). Anthropometric measurements including weight, body weight loss/g, length, body mass index, head circumference and abdominal circumference. Complete systemic examination including gastrointestinal, chest, cardiac and neurological. Complete blood count (CBC) including hemoglobin level (Hb), white blood cells count (WBCs), platelet count using Sysmex KX-21 automatized hematology analyzer (Sysmex corporation, Japan) [17]. Reticulocyte count using Brilliant Cresyl blue stain (Supravital stain). Serum bilirubin (total and direct) using the automated Coombs test (Cobas C 111) (Roche). Also, serum C-reactive protein (CRP) using the latex serology test. Regarding total antioxidant capacity (TAC) levels were measured by Ere's TAC method. In this study, the total blood bilirubin level was measured, and the results were compared before beginning phototherapy, on the first, second, and third days of phototherapy, and 24 hours after ceasing phototherapy.

## Histopathological investigations

Blood samples were collected to conduct histopathological analyses. Using 10-milliliter syringes, blood was drawn into potassium-EDTA tubes (10.5 mg/7 ml). In a chilled centrifuge, blood samples were spun for five minutes at 3000 rpm. The plasma and buffy coat were disposed of. After a 1/10 dilution, packed RBCs were cleaned twice with normal saline to get rid of any leftover leukocytes and plasma components. All reagents were analytical grade. Hexane, 2-thiobarbituric acid (TBA), and trichloroacetic acid (TCA) were obtained from Merck Chemical Company (Darmstadt, Germany).

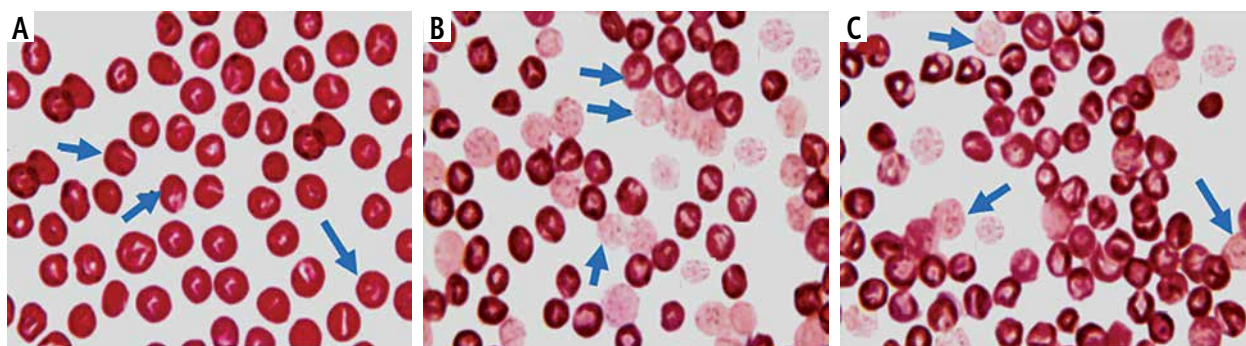
Histopathological investigations indicated that the hemolyzed RBC counts increased in the control group, while vitamin E treatment reduced the hemolyzed RBC count. In the control group, histology of RBCs was normal (Fig. 1A). In the control group, there were remarkable membrane destruction and hemolytic changes in RBCs (Fig. 1B), while in the vitamin VE treated group, these changes were smaller than in the control group (Fig. 1C).

## Morphological evaluation

Using sterile potassium-EDTA tubes to collect blood samples. Giemsa solution was used to stain the blood smears, which were created by spreading one drop of blood onto a slide just after the tubes were inverted and mixed with blood. Using an oil immersion 100/1.25 objective on a Nikon Optiphot-2 microscope (Tokyo, Japan), the morphology of RBCs was ascertained.

## Image analysis

A PC system with hardware and software (Image-Pro Plus 5.0-Media Cybernetics, USA) was used



**Fig. 1. A)** In control group, the morphology of normal RBCs in normal neonates (arrow: normal RBCs, Giemsa; 1150x). **B)** Group C (control) – remarkable membrane destruction and hemolytic changes are seen in the RBCs (arrow: normal RBCs, arrowhead: hemolytic RBCs, Giemsa; 1150x). **C)** In vitamin VE treated neonates, reduced hemolysis of RBCs in vitamin E treated neonates is seen (arrow: normal RBCs, arrowhead: hemolytic RBCs, Giemsa; 1150x)

for image acquisition and analysis, as well as a Spot Insight QE (Diagnostic Instruments, USA) camera and optical microscope. The method required preliminary software procedures of spatial calibration and setting of color segmentation for quantitative color analysis. The image analysis program was used for morphologic evaluation of the samples. The number of intact and hemolyzed RBCs were measured.

### Phototherapy procedure

According to Bhutani *et al.* [18], extensive phototherapy requires two or more lights and uses specialized blue lamps with a peak output at 425-475 nm, known as the most effective for phototherapy. To provide maximum light exposure across the largest possible screen surface area, newborns under phototherapy lights were kept naked aside from eye patches and a face mask used as a diaper. The children were rotated every two hours. When the risk factors for toxicity were eliminated, the baby was old enough to tolerate the bilirubin burden, and the bilirubin level was low enough to no longer raise concerns about toxic effects, phototherapy should be discontinued [18].

### Statistical analysis

Statistical computations were analyzed using SPSS Statistics (SPSS, 25<sup>th</sup> edition, IBM, New York, USA) for Microsoft Windows 10. Two types of statistics were conducted: descriptive statistics that includes the following test as the description of data was in the form of

mean ( $\pm$  SD, median, and range for quantitative data, and frequency and proportion for qualitative data and analytical statistics using Student's *t*-test (*t*), the paired *t* test, and the Mann-Whitney test (*U*) for the quantitative variables, and the chi-square ( $\chi^2$ ) test was used for the qualitative variables. A *p* value < 0.05 was considered significant.

### Results

A flowchart of the study population is shown in Figure 2. In all, 117 neonates with indirect hyperbilirubinemia were enrolled at neonatal intensive care units (NICUs) of the pediatric departments at Al Azhar University Hospitals during the period from February 2021 to October 2022. Nine neonates were excluded from the study (2 patients' parents declined consent and 7 patients did not meet the inclusion criteria). 108 patients were divided into two groups: Group VE (vitamin E; neonatal indirect hyperbilirubinemia was treated with phototherapy and vitamin E at a dose of 25 mg/kg/day for three days in a row beginning on the day of arrival, *n* = 56) and Group C (control; neonatal indirect hyperbilirubinemia while receiving phototherapy without additional vitamin E, *n* = 52). Eight neonates were excluded due to serological conflict manifesting as sepsis, hypersplenism, or bone marrow depression (6 cases from Group VE and 2 cases from Group C) (Fig. 2).

There were no statistically significant differences between the studied groups regarding age (*p* = 0.831), sex (*p* = 0.360), body weight (*p* = 0.120), mode of deliv-

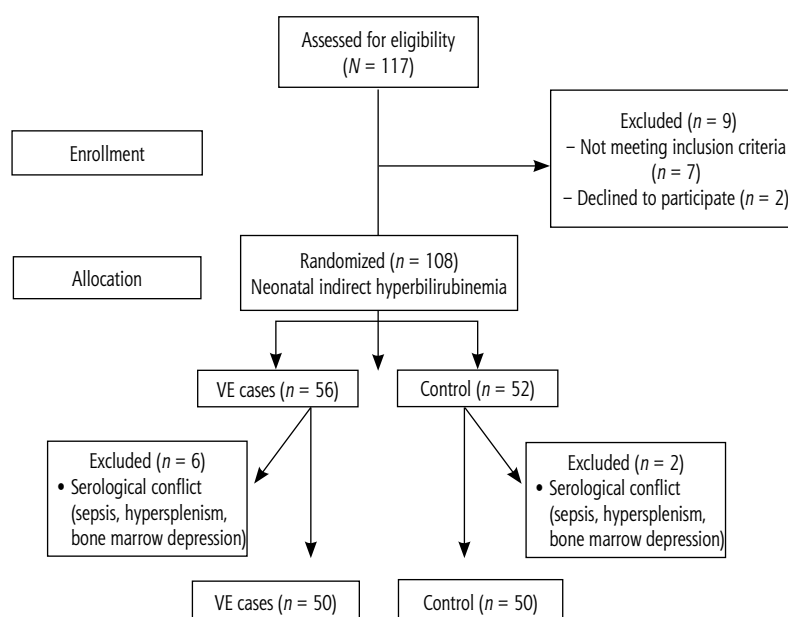


Fig. 2. Flowchart of neonatal indirect hyperbilirubinemia

**Table 1.** Socio-demographic data of the studied neonates

Variable	VE cases (n = 50)	Controls (n = 50)	U test	P value
Age (days)				
Mean ±SD	3.82 ±0.46	3.98 ±0.55	0.170	0.831
Median (range)	3.16 (2-7)	3.5 (3-7)		
Sex, n (%)				
Male	16 (32)	12 (24)	$\chi^2 = 1.49$	0.360
Female	34 (68)	38 (76)		
Body weight (kg)				
Mean ±SD	2.74 ±0.22	3.10 ±0.73	2.67	0.120
Median (range)	2.7 (2.45-3.6)	3 (2.51-3.8)		
Weight loss (g)				
Mean ±SD	280 ±30.76	180.11 ±45.29	58.11	0.014*
Median (range)	250-410	200-290		
Mode of delivery				
	n (%)	n (%)	$\chi^2$	p value
CS	27 (54)	20 (40)	$\chi^2 = 2.85$	0.064
NVD	23 (46)	30 (60)		
Gestational age (weeks)				
Premature	30 (60)	22 (44)	$\chi^2 = 1.93$	0.754
Late preterm	15 (30)	17 (34)		
Full-term	5 (10)	11 (22)		
Nutrition status				
Breastfeeding	30 (60)	25 (50)	$\chi^2 = 0.391$	0.846
Artificial feeding	15 (30)	20 (40)		
Total parenteral nutrition (TPN)	5 (10)	5 (10)		

VE - vitamin E, CS - cesarean section, NVD - normal vaginal delivery, U - Mann-Whitney test,  $\chi^2$  - chi-square test

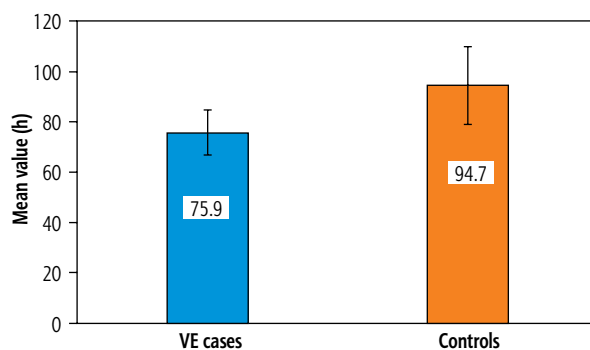
ery ( $p = 0.064$ ), and gestational age in weeks ( $p = 0.754$ ) and nutrition status ( $p = 0.846$ ), but weight loss was significantly higher among VE cases ( $280 \pm 30.76$ ) than controls ( $180.11 \pm 45.29$ ) ( $p = 0.014$ ) (Table 1). There were no statistically significant differences between the studied groups regarding heart rate ( $p = 0.960$ ), respiratory rate ( $p = 0.750$ ) and temperature ( $p = 0.858$ ) (Table 2). Phototherapy exposure was statistically significantly lower among VE cases ( $75.9 \pm 8.95$ ) than controls ( $94.70 \pm 15.42$ ) with a  $p$ -value = 0.004 (Fig. 3). There were no statistically significant differences between the studied groups regarding hemoglobin ( $p = 0.733$ ), total leucocyte count ( $p = 0.080$ ), platelets ( $p = 0.056$ ) and C-reactive protein ( $p = 1.00$ ) (Table 3).

There were statistically significant differences between the studied groups regarding total antioxidant

**Table 2.** Vital signs among the studied neonates

Variable	VE cases (n = 50)	Controls (n = 50)	U test	P value
HR				
Mean ±SD	136 ±15.80	138 ±19.32	0.119	0.960
Median (range)	142 (100-170)	145 (100-180)		
RR				
Mean ±SD	47 ±12.19	54 ±3.10	1.03	0.750
Median (range)	44 (40-60)	51 (40-60)		
Temperature				
Mean ±SD	36.93 ±3.55	37.02 ±4.15	0.165	0.858
Median (range)	35 (36.8-37.9)	36 (36.5-37.5)		

VE - vitamin E, HR - heart rate, RR - respiratory rate, U - Mann-Whitney test,  $\chi^2$  - chi-square test



**Fig. 3.** Phototherapy exposure (h) among the studied neonates

capacity on the third day of admission ( $p = 0.003$ ). Patients treated with vitamin E had higher total antioxidant capacity on the third day of admission ( $0.97 \pm 0.42$ ) than control group ( $0.95 \pm 0.38$ ). Also, among the VE group, total antioxidant capacity was significantly increased on the third day of admission ( $2.75 \pm 0.67$ ) compared to zero days of admission ( $0.97 \pm 0.42$ ) ( $p < 0.001$ ) (Table 4).

There were statistically significant differences between the studied groups regarding serum bilirubin on the third day of admission ( $p = 0.039$ ). Patients treated with vitamin E had lower serum bilirubin on the third day of admission ( $8.25 \pm 3.41$ ) than the control group ( $11.66 \pm 3.22$ ). Also, among VE cases, serum bilirubin was significantly decreased on the third day of admission ( $8.25 \pm 3.41$ ) compared to zero days of admission ( $14.10 \pm 4.39$ ) ( $p = 0.041$ ) (Table 5, Fig. 4).

## Discussion

In the present study, no statistically significant differences between the treated patient and control groups

**Table 3.** Laboratory investigations among the studied neonates

Variable	VE cases (n = 50)	Controls (n = 50)	U test	P value
HB (mg/dl)				
Mean $\pm$ SD	11.45 $\pm$ 3.90	12.23 $\pm$ 4.55	0.205	0.733
Median (range)	11.15 (11-13.66)	12.10 (11.6-14.07)		
TLC ( $\times 10^3/\text{mm}^3$ )				
Mean $\pm$ SD	8300 $\pm$ 35.13	8050 $\pm$ 42.60	2.66	0.080
Median (range)	7900 (5000-11000)	7500 (5000-11200)		
Platelet ( $\times 10^3/\text{mm}^3$ )				
Mean $\pm$ SD	375 $\pm$ 14.20	359 $\pm$ 30.12	3.12	0.056
Median (range)	360 (150-450)	322 (150-450)		
CRP, n (%)				
+Ve	0 (0.0)	0 (0.0)	$\chi^2 = 0.00$	1.00
-Ve	50 (100)	50 (100)		

VE – vitamin E, HB – hemoglobin, TLC – total leucocyte count, CRP – C-reactive protein, U – Mann-Whitney test,  $\chi^2$  – chi-square test

**Table 4.** Total antioxidant capacity among the studied neonates

TAC (mmol)	VE cases (n = 50)	Controls (n = 50)	U test	P value
At admission				
Mean $\pm$ SD	0.97 $\pm$ 0.42	0.95 $\pm$ 0.38	0.266	0.751
Median (range)	0.93 (0.9-1.2)	0.90 (0.73-1.1)		
3rd day of admission				
Mean $\pm$ SD	2.75 $\pm$ 0.67	0.98 $\pm$ 0.33	9.88	0.003*
Median (range)	266 (1.63-3.7)	0.94 (0.79-1.2)		
% Different	183.5%	3.2%		
Mean diff.	1.78 $\pm$ 0.25	0.03 $\pm$ 0.05		
Paired t test	9.52	0.290		
P value	< 0.001*	0.74		

VE – vitamin E, U – Mann-Whitney test, t –paired t test, \*Significant

**Table 5.** Serum bilirubin among the studied neonates

Serum bilirubin (mg/dl)	VE cases (n = 50)	Controls (n = 50)	U test	P value
At admission				
Mean $\pm$ SD	14.10 $\pm$ 4.39	14.7 $\pm$ 5.67	14.7 $\pm$ 5.67	0.982
Median (range)	13.88 (12-17)	14.19 (13-18)		
3 <sup>rd</sup> day of admission				
Mean $\pm$ SD	8.25 $\pm$ 3.41	11.66 $\pm$ 3.22	3.98	0.039*
Median (range)	8 (7-10)	11.3 (10-13)		
% Different	70.9%	26.1%		
Mean diff.	5.85 $\pm$ 0.98	3.04 $\pm$ 2.45		
Paired t test	3.85	1.16		
P value	0.041*	0.70		

VE – vitamin E, U – Mann-Whitney test, t –paired t test, \*Significant

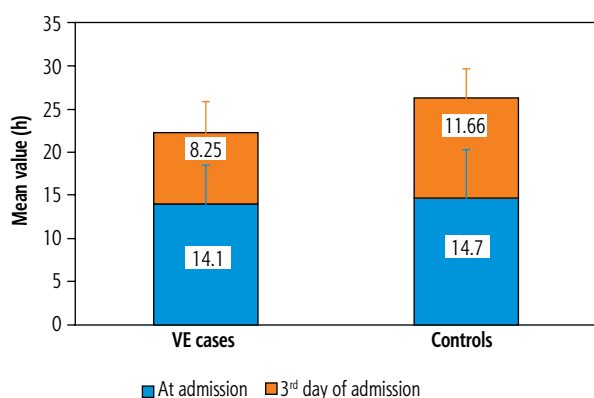


Fig. 4. Serum bilirubin distribution among the studied neonates

regarding age, sex, body weight and mode of delivery were found. Our results agree with Stevenson *et al.* [19], who reported that infants in the vitamin E-treated group had a male : female ratio of 12 : 7, a mean birth weight of 1272 g, and a mean gestational age of 29 weeks. The M : F ratio in the control group was 11%, and the differences between the vitamin E-treated and control-treated groups were not statistically significant. The control group's mean birth weight was 1214 g, and its mean gestational age was 29 weeks. Another study was done by Abdul-Razzak *et al.* [20], who studied the correlation between full-term newborns' hyperbilirubinemia severity and plasma vitamin E and C levels. In 119 newborns who did not develop hyperbilirubinemia and 11 neonates who did develop substantial hyperbilirubinemia, the concentrations of the vitamins E and C in the blood were evaluated on the first day of life. There was no discernible difference between the two groups' gestational ages and birth weights. Also, El Mashad *et al.* [21] evaluated the impact of vitamin E supplementation in the management of secondary hyperbilirubinemia in newborns receiving phototherapy. They discovered that statistical examination of the data revealed no statistically significant differences between the vitamin E supplementation group and the control group in terms of age, sex, or body weight. This suggests that the cases were carefully chosen. Thiagarajan *et al.* [22] assessed neonates who were receiving phototherapy for newborn jaundice and their oxidative stress. They discovered that there were 26 males and 14 females among the controls and 25 males and 15 females among the neonates who were enrolled as cases. The two groups' distributions of age and sex were comparable.

In the current study, treated patients had significantly lower exposure to phototherapy than the control group. These results are in agreement with the results obtained by Gross [23], who studied 20 neonates

with a birth weight of 2500-3500 g. The vitamin E supplemented group also experienced significantly shorter phototherapy sessions. These disparities were not as noticeable in newborns who weighed more than 2500 g at birth. Also, these results are in agreement with Akisü *et al.* [24], who needed 72 hours of continuous phototherapy to assess the antioxidant defense system in neonates undergoing phototherapy. They found no significant change in serum levels of vitamin E before and 72 hours after the phototherapy. On the other hand, our results disagree with Hadjigeorgiou *et al.* [25], who studied 11 full-term infants with jaundice who received phototherapy and had their serum vitamin E levels measured and compared to 10 full-term jaundiced control children. They discovered that no alterations were seen prior to, during, or one week after quitting phototherapy. Regarding the values of microhematocrit, hemoglobin, and reticulocytes, the two groups of babies both showed poor outcomes.

In our study, no statistical differences were found between the studied groups regarding CBC including hemoglobin, TLC, platelet, and CRP. These results agree with Westergren and Betty [26], who found that in both control-supplemented and vitamin E-supplemented groups, hemoglobin levels between the two groups did not significantly differ at any point in time. A control-supplemented infant also attained vitamin E adequacy and a decline in bilirubin generation by day 7 of life; vitamin E supplementation considerably increases vitamin E levels. Ferlin *et al.* [27], however, reported that since this supplementation did not change hemoglobin levels, the prophylactic or therapeutic use of vitamin E, 25 IU/day, had no impact on early anemia of preterm. Also, Hadjigeorgiou *et al.* [25] found no differences before or after phototherapy or 1 week after stopping it. The same negative results were noted in the two groups of infants about the values of microhematocrit, hemoglobin, and reticulocytes. On the other hand, Gross *et al.* [23] found from day 3 to day 8 that the treatment group's mean percent carboxyhemoglobin level dramatically decreased (1.08-0.78%), whereas the control group's mean value stayed constant at 0.96%. Vitamin supplementation appears to slow down but not stop the rapid red cell death that is unique to preterm infants. Similarly, Abdul-Razzak *et al.* [20] found that neonates with hyperbilirubinemia had considerably decreased hemoglobin and hematocrit levels. The study done by Abd El Wahed *et al.* [28] found that preterm neonates may benefit from receiving additional vitamin E supplements as vitamin E may be able to prevent or reduce some preterm complications.

Our patients treated with phototherapy had decreased serum bilirubin on the third day of admission and had a higher rate of bilirubin decline than control group. Also, serum bilirubin on the third day of admission was significantly lower than at zero days of admission. These results agreed with those obtained by Gross *et al.* [23], who found that vitamin E-treated newborns who had birth weights under 2500 g showed a substantial reduction in serum bilirubin on day 3 of life as well as a significant reduction in peak serum bilirubin over the first week of life. Our finding is also like that of Kaplan *et al.* [29], who concluded that vitamin E deficiency may be the cause of the significant hyperbilirubinemia and enhanced hemolysis seen in newborn jaundice. These results agreed with those obtained by Ojo *et al.* [30], who observed a significant decrease plasma vitamin E level in full-term neonates associated with an increase in bilirubin level and red blood cell hemolysis. These results agree with Fischer *et al.* [31], who found that each neonate's serum total bilirubin levels were measured on the first and third study days, and there was a favorable link between those levels and vitamin E administration. In contrast, our results disagree with Westergren and Betty [26], who found that when compared to day 1, vitamin E levels were significantly higher on days 3 and 7. On day 3 compared to day 1, neither group's bilirubin production differed considerably. However, by day 7, both groups' bilirubin production had decreased dramatically compared to day 1. At any given moment, there were no appreciable variations in the two groups' serum bilirubin levels. A control-supplemented infant also attained vitamin E adequacy and a decline in bilirubin generation by day 7 of life; vitamin E supplementation considerably increases vitamin E levels. Meanwhile, Dani *et al.* [32] found in preterm newborns that lower plasma bilirubin levels were associated with lower plasma antioxidant capacity and higher levels of oxidative stress. These observations could result from heme oxygenase's pro-oxidant activity brought on by the release of iron. Another study by Thiagarajan *et al.* [22] found that mean total serum bilirubin levels were  $10.13 \pm 2.47$  mg/dl for controls,  $17.85 \pm 1.82$  mg/dl for cases in the pre-phototherapy study group, and  $15.19 \pm 1.56$  mg/dl for cases in the post-phototherapy study group. It demonstrates that phototherapy treatment dramatically reduced the level of total serum bilirubin. Similarly, El Mashad *et al.* [21] found there were no differences in serum bilirubin levels on days 1 or 3 between the groups receiving vitamin E and the control group. On days 1 and 3, they continued to notice no variations in serum bilirubin levels. The findings of their study indicate that in premature newborns

weighing less than 1500 g at birth, supplementary oral vitamin E therapy had no appreciable impact on bilirubin generation during the first three days of life.

Our patients treated with vitamin E had higher TAC on the third day of admission than control group. Also, TAC on the third day of admission was significantly higher than at zero days of admission. Also, the treated group had a significantly higher rate of TAC increase than the control group. These results agree with those obtained by Abd El Wahed *et al.* [28], who found that preterm neonates may benefit from receiving additional vitamin E supplements as vitamin E may be able to prevent or reduce some preterm complications. Also, El Mashad *et al.* [21] found that in the groups under study, there was no appreciable difference in TSB upon admission. This suggests careful case selection. However, the studied groups' TSBs at discharge showed a highly significant difference. When compared to group III, which received only phototherapy, group I, which received 25 mg/kg/day of oral vitamin E along with phototherapy, had significantly higher TSB at discharge; however, there was no discernible difference between group II, which received 50 mg/kg/day of oral vitamin E along with phototherapy, and groups II and III.

## Conclusions

In conclusion, vitamin E supplementation has an important role in treatment of indirect hyperbilirubinemia. Early administration of vitamin E in preterm neonates resulted in a significant decrease of serum bilirubin and increased total antioxidant capacity. Vitamin E supplementation in full term decreases duration of phototherapy. Further investigational studies about the role of vitamin E on pathological hyperbilirubinemia are needed. Future studies are needed to examine preterm and term neonates separately with larger sample sizes.

## Disclosure

The authors declare no conflict of interest.

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