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Study of Vitamin D and melatonin supplementation as adjuvant therapies in neonatal jaundice.

Mohamed Shawky Elfarargy[1]*, Dina Adam Ali[2], Ghada Mohammad Al-Ashmawy[3]

[1]Faculty of Medicine, Department of Pediatrics, Tanta University, Egypt
[2]Faculty of Medicine, Department of Clinical Pathology, Tanta University, Egypt
[3]Faculty of Pharmacy, Department of Biochemistry, Tanta University, Egypt

Abstract

Background: Neonatal jaundice is a common problem in neonates which is treated by various methods to avoid the development of complication especially bilirubin encephalopathy or kernicterus.

Patient and methods: This is a prospective clinical trial was done from July 2016 to January 2018 in Tanta University Hospital on 150 neonates suffering from neonatal jaundice. The studied neonates were divided into 3 Groups: Group 1 who was treated by vitamin D and phototherapy, Group 2 who were treated by melatonin and phototherapy and Group 3 who were treated by phototherapy alone.

Results: The serum bilirubin was significantly declined in neonates of group 1 who were treated by vitamin D and phototherapy, compared with neonates of Group 2 and 3 who were treated with combined melatonin with phototherapy and phototherapy, respectively with p-value equal 0.009* and 0.001* respectively. There was a significant decrease in serum bilirubin levels in neonate of Group 2 who was treated with melatonin and phototherapy if compared with Group 3 who was treated by phototherapy alone with p-value equal 0.003*.

Conclusion: Vitamin D and melatonin could be used as adjuvant therapies in neonatal jaundice in combination with phototherapy with superiority of vitamin D over melatonin.

Keywords: Neonates, Jaundice, Vitamin D, Melatonin.

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Introduction

Neonatal jaundice or neonatal indirect hyperbilirubinemia is a very common condition all over the world and is considered one of the most important problems in neonates especially when the levels of indirect bilirubin increased to levels that could pass the blood brain barrier which can lead to bilirubin encephalopathy or kernicterus if untreated as early as possible [1].

The neonatal jaundice is defined clinically as yellow color of the skin of the body and also the mucus membrane, in addition to the eyes especially the sclera due to the rise of the serum bilirubin levels, it is either physiological which did not rise to high levels or pathological which rises to high levels. Pathological jaundice may be affected by different parameters such as gestational age, birth weight, premature rupture of membranes, maternal infectious disorders or other diseases during pregnancy, [1].

There are numerous of reasons of neonatal jaundice or neonatal hyperbilirubinemia which include blood Group incompatibility, Rh incompatibility, glucose-6-phosphate dehydrogenase deficiency and elevated the red blood cells mass. There are several treatment modalities which were used in the management of pathological jaundice in neonates including phototherapy, exchange blood transfusion and intravenous immunoglobulin but there are many side effects to these lines of treatment in addition to difficulties and serious risks of some lines of treatment especially the exchange blood transfusion. So, the need of new lines of treatment that could be used as adjuvant therapies to the previous old established lines of treatment of neonatal jaundice had been essential to protect the neonates from the serious effect of the increased levels of bilirubin which may lead to bilirubin encephalopathy or kernicterus [2].

Vitamin D is a fat-soluble vitamin which has an important function in the body especially in the teeth and bone formation in infants and children. The liver plays a very important role in the synthesis of vitamin D in neonates and also the liver plays a major role in bilirubin metabolism by conversion of unconjugated bilirubin which could pass the blood brain barrier to conjugated bilirubin [3].

In addition, the 25-hydroxylation phase, one of the core phases of vitamin D biosynthesis, occurs in the liver, as well as bilirubin conjugation [4]. Melatonin is a physiological indoleamine which is secreted from the pineal gland into the blood. This hormone has antioxidant effects; it is synthesized mainly in the pineal gland from the amino acid tryptophan. Melatonin has a marvelous effect in prevention and treatment of liver injuries and diseases by its antioxidant effect which protects the liver from the hazardous effect of these oxidants [5].

The liver action includes detoxification of large amounts of reactive oxygen species which are generated in the body and they exert a toxic effect on hepatocytes. A valuable and beneficial antioxidant action which is done by melatonin and has an important role in prevention of the toxic effects of these oxidants like oxygen free radicals on the liver. The healthy liver also is the site for detoxification and conjugation of the indirect bilirubin to direct bilirubin [6].

The aim of this research is to study the effect of vitamin D and melatonin supplementation as adjuvant therapies in cases of neonatal jaundice.

Patient and Methods

This is a prospective clinical trial was done from July 2016 to January 2018 in Tanta University Hospital on 150 neonates suffering from neonatal jaundice after approval by the Ethical Committee of Faculty of Medicine, Tanta University and informed consents were taken from the parents of all neonates included in the study. These studied neonates were divided into 3 Groups as follows:

Group 1 (n=50)

Neonates of this Group were full term admitted with indirect hyperbilirubinemia from 14-20 mg/dl at 3rd day of life who received phototherapy and also received 10 drops of vitamin D (1000 IU) once daily for 5 days in the form of Vidrop® (Medical Union Pharmaceuticals, Egypt) [7].

Group 2 (n=50)

Neonates of this Group were full term admitted with indirect hyperbilirubinemia from 14-20 mg/dl at 3rd day of life who received phototherapy and also received melatonin in a dose of 10 mg/kg once daily for 5 days. Melatonin tablets (3 mg per tablet; Puritan's Pride®, Oakdale, NY, USA) were crushed, then dissolved in 5 ml of distilled water and administered via orogastric tube [8].

Group 3 (n=50)

Neonates of this Group were full term admitted with indirect hyperbilirubinemia from 14-20 mg/dl at 3rd day of life who received phototherapy only.

Inclusion criteria

full term neonates, admitted to the incubator at the third day of life suffering from indirect hyperbilirubinemia with total serum bilirubin from 14-20 mg/dl, all the 3 Groups were treated with phototherapy in addition to vitamin D and melatonin in Group 1and 2, respectively.

Exclusion criteria

Preterm neonates, conjugated hyperbilirubinemia, neonatal sepsis, neonatal hypoxia, neonatal respiratory distress, congenital anomalies, liver or kidney disease in the neonates or their mothers.

Biochemical assays

A venous blood sample (4 ml) was withdrawn from each neonate using a sterile BD vacutainer butterfly needle. Each blood sample was divided into two portions (2 ml each). The first portion was collected in a tube containing 4 mg of potassium-ethylene diamine tetraacetic acid (K2EDTA) for reticulocytes percent and hemoglobin level determination. The second portion was collected in a BD vacutainer serum separator tube, and serum samples were separated after centrifugation and stored at -20°C until total bilirubin levels were assessed.

Reticulocytes percent and hemoglobin level were assayed using an automated hematology analyzer (Sysmex® XT-1800I, Japan). Serum total bilirubin was measured, according to the manufacturer's instructions (Roche® Diagnostics, Germany) using the colorimetric method.

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Science (SPSS) version 20. Data were expressed as mean ± SD. Statistical comparison among Groups was performed by t-test, Chi-square (X2) test for comparison between two Groups. Statistical significance was set at p-values >0.05.

Results

This study was done on 150 neonates suffering from neonatal jaundice, the studied neonates were divided into 3 Groups: Group 1 who was treated by vitamin D and phototherapy and Group 2 who were treated by melatonin and phototherapy and Group 3 who were treated by phototherapy alone.

This table showed comparison between the 3 Groups as regard weight (kg), gestational age (Weeks), bilirubin levels (mg/dl), hemoglobin levels (gm/dl), reticulocytic count (%), mode of delivery and sex where there were no significant difference between the 3 Groups (Table 1).

This table showed comparison between the 3 Groups as regard weight (kg), gestational age (weeks), bilirubin levels (mg/dl), hemoglobin levels (gm/dl), reticulocytic count (%), mode of delivery and sex where there were no significant difference between the 3 Groups (Table 2).

This table showed comparison between the 3 Groups as regard serum bilirubin from the 2nd to the 6th day of admission where there was no significant difference between the 3 Groups in the 2nd, 3rd and 4th day of admission while there were significant differences between the 3 Groups in the 5th and 6th day of admission (Table 3).

This table showed comparison between the 3 Groups as regard serum bilirubin at the 7th day of admission where there was significant difference between them with p-value is 0.001*, significant difference between Group 1 and Group 3 with p-value is 0.001*, significant difference between Group 2

Table 1. *Comparative characteristics between studied groups on admission (3rd day of life).*

Variables		Group 1 (n=50)		Group 2 (n=50)		Group 3 (n=50)		F-test	p-value
Weight (kg)	Mean ± S.D	3685.4 ± 95		3667.6 ± 125.4		3649.1 ± 111.8		1.056	0.294
Gestational Age (Weeks)	Mean ± S.D	39.2 ± 1.3		39.1 ± 1.2		39.3 ± 1.4		0.358	0.468
Bilirubin levels (mg/dl)	Mean ± S.D	17.10 ± 2.6		17.14 ± 2.8		17.15 ± 2.7		0.123	0.685
Hemoglobin levels(gm/dl)	Mean ± S.D	14.2 ± 0.8		14.1 ± 0.9		14 ± 0.9		0.859	0.362
Reticulocytic count (%)	Mean ± S.D	7.65 ± 0.55		7.55 ± 0.45		7.6 ± 0.50		0.569	0.426
Variables		**N**	**%**	**N**	**%**	**N**	**%**	**X2**	**p-value**
Mode of delivery	NVD	18	36	19	38	17	34	0.168	0.917
	CS	32	64	31	62	33	66		
Sex	Male	26	42	28	46	27	44	0.163	0.923
	Female	24	48	22	44	23	46		

**p-value is significant if < 0.05 NVD: Normal Vaginal Delivery. CS: Cesarean Section.*

Table 2. *Comparison of the studied groups as regard serum bilirubin on admission and at 7 days of admission.*

Variables		At 3rd day of life (1st day of admission)	At the 10th day of life (7th day of admission)	t.-test	p-value
Serum bilirubin (mg/dl)	Group 1	17.10 ± 2.6	7.1 ± 1	25.379	0.001*
	Group 2	17.14 ± 2.8	7.9 ± 0.8	22.443	0.001*
	Group 3	17.15 ± 2.7	8.9 ± 0.7	20.912	0.001*

**p-value is significant if <0.05.*

Table 3. *Comparison between group 1, 2 and 3 as regard serum bilirubin between the 2nd and 6th day of admission.*

Variables	Group 1	Group 2	Group 3	F-test	p-value
Time(Days)	Serum bilirubin (mg/dl)				
2nd day of admission	15.7 ± 2.1	15.8 ± 2.2	15.9 ± 2.2	0.136	0.643
3rd day of admission	14.4 ± 1.8	14.5 ± 1.9	14.7 ± 1.8	0.521	0.407
4th day of admission	12.8 ± 1.5	13 ± 1.4	13.4 ± 1.6	1.324	0.105
5th day of admission	11.1 ± 1.2	11.4 ± 1.1	12 ± 1	4.526	0.013*
6th day of admission	9 ± 1.1	9.6 ± 1	10.3 ± 0.9	12.635	0.001*

**p-value is significant if <0.05.*

Table 4. *Comparison between group 1, 2 and 3 as regard serum bilirubin at the 7th day of admission.*

Serum bilirubin (mg/dl) at the 7th day of admission	Group 1 (n=50)	Group 2 (n=50)	Group 3 (n=50)
Mean ± SD	7.1 ± 1	7.9 ± 0.8	8.9 ± 0.7
F-test	15.327		
p-value	0.001*		
Group 1 and Group 2	Group 1 and Group 3		Group 2 and Group 3
0.009*	0.001*		0.003*

**p-value is significant if <0.05.*

and Group 3 with p-value is 0.003* and significant difference between Group 1 and Group 2 with p-value is 0.009* (Table 4).

Discussion

Neonatal jaundice or neonatal indirect hyperbilirubinemia is a common disease in neonates which is caused by many different causes. The neonatal jaundice may be physiological or pathological causing many serious problems especially bilirubin encephalopathy or kernicterus which had many dangerous squeals like cerebral palsy, mental retardation, deafness and permanent brain damage [9].

The treatment of pathological neonatal jaundice had some side effects especially the exchange blood transfusion which may cause thrombosis, hemorrhage, transmission of diseases and serious reactions from the exchanged blood, so there may be a need for searching about some adjuvant therapies that could be used as an adjuvant therapy with phototherapy which is used in the treatment of pathological neonatal jaundice [10].

This study was done on 150 neonates suffering from neonatal jaundice, the studied neonates were divided into 3 Groups: Group 1 who was treated by vitamin D and phototherapy and Group 2 who were treated by melatonin and phototherapy and Group 3 who were treated by phototherapy alone.

This study showed that the comparison between the 3 Groups as regard serum bilirubin at the 7th day of admission where there was significant difference between them with p-value is 0.001*, significant difference between Group 1 and Group 3

with p-value is 0.001*, significant difference between Group 2 and Group 3 with p-value is 0.003* and significant difference between Group 1 and Group 2 with p-value is 0.009*.

This study revealed that vitamin D administration to neonates with pathological neonatal jaundice was accompanied by improvement in the levels of serum bilirubin and the Group which is treated with vitamin D and phototherapy was accompanied by significant decrease in the levels of the serum bilirubin if compared with Group which is treated by phototherapy alone which may indicate that vitamin D is important in the reduction of the serum bilirubin in neonates with pathological jaundice.

In agreement with this study which revealed the importance of vitamin D in neonates with hyperbilirubinemia, there was study which stated that levels of serum vitamin D in neonates were significantly lower in neonates with pathological jaundice if compared with control non-jaundiced Group which may indicate a strong relationship and significant negative correlation between the levels of serum bilirubin and serum vitamin D levels in neonates [11].

Vitamin D was proven to play an important role in liver metabolism through hydroxylation of the vitamin D in the liver. The liver tissue is the cornerstone for activation of vitamin D through hydroxylation of Cholecalciferol which is converted in the liver to calcifediol (25-hydroxycholecalciferol) and also the liver is responsible for the synthesis and conjugation of bilirubin, some studies had revealed that the decreased serum levels of vitamin D might be associated with the occurrence of neonatal jaundice [6].

In spite of that the pathway of metabolism of vitamin D and bilirubin were performed on two pathways, but both pathways had a common pathway in the liver and the presence of good supplementation of vitamin D will help the liver metabolism and the changes in metabolism or synthesis of each of them might have an impact on the metabolism and the synthesis of the other [12]. In disagreement with our study which revealed that vitamin D administration with phototherapy to pathologically jaundiced neonates was associated with significant decrease in serum bilirubin in neonates if compared to neonates who were treated by phototherapy alone, there was a study which stated that there was no relationship between the neonatal serum vitamin D levels and neonatal indirect hyperbilirubinemia [13]. This study tried to examine the effect of melatonin administration to the neonates on the levels of serum neonatal bilirubin and explain if the melatonin could help in the reduction of serum bilirubin in neonates suffering from pathological neonatal jaundice.

Melatonin administration had various and multiple advantages and benefits in liver functions and the melatonin which prevent the oxidative stress and support the liver functions where bilirubin metabolism and conjugation of unconjugated or indirect bilirubin to conjugated or direct bilirubin though decreasing the indirect hyperbilirubinemia [5]. Melatonin has an important role in improvement of hepatic microcirculation, melatonin administration has many protective effects on liver tissues and promotes adequate liver functions including bilirubin metabolism [14].

Melatonin is mainly accumulated in a high concentration in the liver, and the metabolism of the melatonin occur only in the liver and also the bilirubin metabolism occurs in the liver and the changes in metabolism of each of them might have an impact on the metabolism of the other. Melatonin acts as potent and effective antioxidants that help in protecting liver tissues and maintaining the liver functions including bilirubin metabolism which help in reducing indirect bilirubin levels in the serum by bilirubin conjugation, and fortunately the melatonin metabolites also have potent and good anti-oxidative function which help in more protection of liver tissues structure and function. The melatonin does its anti-oxidative effects either through its radical scavenging functions or via activation of antioxidant enzymes [15].

The liver plays an important role in the metabolism and detoxification of various substances in the body. During the metabolism and detoxification of some substances there will be production of reactive oxygen species which produce a toxic effect on hepatotoxic effects which affect the liver function in the metabolism of various substances like bilirubin metabolism, the melatonin which is a potent antioxidant through various mechanisms will protect the liver tissues and maintaining excellent liver functions [16].

Melatonin (10 mg/kg body weight) act as potent and beneficial antioxidant which prevent the rise in mitochondrial peroxidase activity and prevent the elevation of nitric oxide level in plasma protecting the liver tissues structure and functions, after melatonin administration, the increase in serum SGPT and SGOT levels was significantly decreased and liver functions and structures was improved [17,18].

Conclusion

This study concluded that vitamin D and melatonin could be used as adjuvant therapies in neonatal jaundice in combination with phototherapy with superiority of vitamin D over melatonin.

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Correspondence to:

Mohamed Shawky Elfarargy
Assistant Professor of Pediatrics,
Faculty of Medicine,
Tanta University, Tanta,
El-Gharbia, Egypt.
Tel: 0201005171750
E-mail: farargy2009@hotmail.com