Research Article

Fenofibrate and Antioxidant Vitamins [D, E and C] as Anovel Approach in Treatment of Uncomplicated Neonatal Hyperbilirubinemia.

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Abstract
Introduction: Neonatal jaundice refers to the yellow coloration of the skin and sclera of newborn babies that results from the deposition of bilirubin (Woodgate and Jardine, 2015). **Aim of the work:** The aim of this study was to evaluate the efficacy of oral use of fenofibrate, vitamin D and other antioxidant vitamins (E and C) in the treatment of indirect neonatal hyperbilirubinemia. **Patient and Methods:** This Case control study was carried on 80 fullterm neonates suffering from neonatal jaundice admitted to the Neonatal Intensive Care Unit in Minia University Hospital and El-Minia General Hospital from January 2015 to May 2016. **Results:** This study included 80 full term (FT) neonates admitted to the "NICU" of Minia University Pediatric Hospital and Minia General Hospital suffering from neonatal indirect hyperbilirubinemia, from January 2015 till May 2016. The study included 80 full term neonates (36 - 42wks): (54 males and 26 females), (45 ABO incompatibility, 6 Rh incompatibility and 29 exaggerated physiological jaundice). These neonates were allocated into four groups. The results are shown in tables and figures. **Conclusion:** In conclusion, addition of single oral dose of fenofibrate in jaundiced baby receiving phototherapy in first 24h of treatment can significantly reduce the serum bilirubin levels in term newborns and duration of phototherapy .
Keywords: Antioxidant Vitamins [D, E And C].

Introduction
Neonatal jaundice refers to the yellow coloration of the skin and sclera of newborn babies that results from the deposition of bilirubin[(1)].

Jaundice is the most common condition requiring medical attention in newborn babies. About 50% of term and 80% of preterm babies develop jaundice in the first week of life. Jaundice is also a common cause of re-admission to hospital after early discharge of newborn babies. Jaundice usually appears 2 to 4 days after birth and disappears 1 to 2 weeks later, usually without the need for treatment[(2)].

As assessed by population-based studies and registries, the incidence of severe hyperbilirubinemia in High-Income Countries (HICs) is estimated to be about 31.6/100,000 live births, while the incidences of Acute Bilirubin Encephalopathy (ABE) and kernicterus/Chronic Bilirubin Encephalopathy (CBE) have been estimated as being in the range of 1.0-3.7 and 0.4-2.7/100,000 live births, respectively[(3)].

On the contrary in Low- And Middle-Income Countries (LMICs) there is no harmonized protocols for hyperbilirubinemia classification and management have been implemented leading to wide variations in protocols and rendering difficult if not impossible comparisons between different locations, with the exception of Malaysia and Egypt which adopted the American Academy of Pediatrics (AAP) guidelines for neonatal jaundice (NNJ) management. Despite these limitations, the prevalence is said to be high in LMICs, where records and documentation of the incidence of NNJ, ABE and CBE are usually poor and variable[(4)]. The African region has the highest incidence of severe neonatal jaundice (SNJ) per 10 000 live births at 667.8 ,while Eastern Mediterranean at 165.7[(5)].

Aim of the work
The aim of this study was to evaluate the efficacy of oral use of fenofibrate, vitamin D and other antioxidant vitamins (E and C) in the

treatment of indirect neonatal hyperbilirubinemia.

Patient and Methods

This Case control study was carried on 80 fullterm neonates suffering from neonatal jaundice admitted to the Neonatal Intensive Care Unit in Minia University Hospital and El-Minia General Hospital from January 2015 to May 2016.

Inclusion criteria:

- Gestational age of 36 – 42 weeks.
- Indirect serum bilirubin ranges from 15 to 20 mg/dl.
- Birth weight ranges from 2000g to 3500 g.

Exclusion criteria:

- Gestational age < 36 weeks.
- Conjugated bilirubin above 20% of total serum bilirubin or > 2 mg/dl.
- Sepsis.
- Low birth weight < 2000g.

Parental consent:

Before randomization, written parental consent was obtained for each eligible infant to participate in the study.

Study Design:

This Case control study was carried on 80 full term (FT) neonates admitted to the "NICU" Minia University Pediatric Hospital and Minia General Hospital suffering from neonatal indirect hyperbilirubinemia. These neonates were randomly allocated into four groups. We used random allocation cards using computer-generated random numbers.

The permission of their parents and the ethical committee of hospital were taken.

- All four groups received phototherapy under standard conditions. In order to minimize possible bias due to different types of phototherapy machines, we used only one type of phototherapy machine adjusted to 25cm above the infants 'incubators. The irradiance of the phototherapy lights was monitored weekly to be maintained at 20–30 µW/cm 2 per nm with four special white 420-480 nm lamps.
- All infants were monitored continuously with a pulse oximeter (Nellcore Pleasanton, USA) and their axillary temperature was checked at 4 hours intervals. Phototherapy was ceased when indirect serum bilirubin was ≤ 12 - 13 mg/dl.
- They were fully exposed except their eyes and nappy areas.
- Breastmilk was used as can as possible together with artificial milk. The artificial milk used was full strength humanized formula given every 3hours (8 feeds / 24 hours), the amount/feed depended on the infant's tolerance.

Group (A):

Which included 20 neonates who received phototherapy with entral feeding only.

Group (B):

Which included 20 neonates who received phototherapy with entral feeding and single oral dose of fenofibrate suspension with a dose 10 mg/kg beside phototherapy.

Result:

This study included 80 full term (FT) neonates admitted to the "NICU" of Minia University Pediatric Hospital and Minia General Hospital suffering from neonatal indirect hyperbilirubinemia, from January 2015 till May 2016. The study included 80 full term neonates (36 - 42wks): (54 males and 26 females), (45 ABO incompatibility, 6 Rh incompatibility and 29 exaggerated physiological jaundice). These neonates were allocated into four groups. The results are shown in tables and figures.

Control group A:

Including 20 neonates (13 male & 7 female) with unconjugated hyperbilirubinemia.

All neonates in this group received only phototherapy as controls.

Group B:

Including 20 neonates (14 male & 6 female) with unconjugated hyperbilirubinemia.

All the neonates in this group recieved single oral dose of fenofibrate suspension in a dose 10 mg/kg beside phototherapy.

Group C:

Including 20 neonates (13 male & 7 female) with unconjugated hyperbilirubinemia.

All the neonates in this group received phototherapy and daily dose of vitamin D (400 IU/24h).

Group D:
Including 20 neonates (14 male & 6 female) with unconjugated hyperbilirubinemia.

All the neonates in this group recieved phototherapy, daily dose of vitamin E (4 mg/day) and daily dose of viamin C (40 mg/day).

The duration of hospital stay of control and fenofibrate groups:

Duration of stay	Controls Group	Fenofibrate group	P-value
2 days	0	10(50%)	
3 days	1(5%)	7(35%)	
4 days	4(20%)	3(15%)	
5 days	9(45%)	0	
6 days	5(25%)	0	
7 days	1(5%)	0	
Range	3-7	2-4	0.001*
Mean ±SD	5.05±0.9	2.6±0.7	

The mean duration of stay at hospital of fenofibrate group was 2.6±0.7 days shorter than the mean duration of stay at hospital of control group which was 5.05±0.9 days with significant P value = 0.001*.

Demographic and clinical data of the studied groups (controls, fenofibrate, vit D and vit C&E):

Data	variable	Group A (control)	Group B (fenofibrate)	Group C (Vit D)	GroupD (vit E&C)	P-value		
						A vs B	A vs C	A vs D
Sex	Male	13(65%)	14(70%)	13(65%)	14(70%)	0.7	0.9	0.7
	Female	7(35%)	6(30%)	7(35%)	6(30%)	0.7	0.9	0.7
Weight in Kg	<3kg	12(60%)	10(50%)	12(60%)	13(65%)	0.5	0.9	0.7
	>3kg	8(40%)	10(50%)	8(40%)	7(35%)	0.5	0.9	0.7
Blood group of baby	A	11(55%)	7(35%)	8(40%)	10(50%)	0.6	0.7	0.8
	B	5(25%)	7(35%)	6(30%)	4(20%)	0.4	0.7	0.5
	AB	2(10%)	3(15%)	4(20%)	2(10%)	0.6	0.8	0.8
	O	2(10%)	3(15%)	2(10%)	4(20%)	0.6	0.7	0.8
Highest serum levels of indirect bilirubin (mg /dl)	15 – 16	1(5%)	4(20%)	5(25%)	3(15%)	0.3	0.3	0.8
	16 – 17	8(40%)	4(20%)	5(25%)	6(30%)	0.3	0.4	0.6
	17 – 18	4(20%)	6(30%)	6(30%)	5(25%)	0.3	0.3	0.7
	18 – 19	3(15%)	4(20%)	2(10%)	3(15%)	0.3	0.3	0.7
	19 – 20	4(20%)	2(10%)	2(10%)	3(15%)	0.2	0.5	0.8
Mode of delivery	SVD	13(65%)	9(45%)	14(70%)	12(60%)	0.2	0.7	0.
	CS	7(35%)	11(55%)	6(30%)	8(40%)			1

SVD = Spontaneous Vaginal delivery C.S = Caesarean Section.

Showed that male neonates presents > 60% of cases but there were no significant statistical differences between the studied groups as regard sex, age on admission, gestational age, mode of delivery, blood groups and weight.

Discussion

Neonatal jaundice (NNJ), is usually benign, but in some cases it can progress to severe hyper-bilirubinemia, acute bilirubin encephalopathy (ABE) and kernicterus/chronic bilirubin ence-phalopathy (CBE). ABE and CBE are largely preventable if severe hyperbilirubinemia is identified early and treated promptly[6].

Guidelines for managing jaundice have been proposed by the American Association of Pediatrics (AAP), the UK National Institute for

Health and Care Excellence (NICE) and others[7].

Although timely use of high performance phototherapy devices has been established in the effective management of neonatal hyperbilirubinemia (NHB), the condition still remains a leading cause of morbidity and mortality in resource-constrained settings[8].

The aim of this study was to compare between the effect of phototherapy alone and phototherapy together with oral fenofibrate, vitamin D or vitamin C&E on indirect serum bilirubin level in neonates with hyperbilirubinemia to decrease the duration of stay at NICU.

This study was performed in Minia Neonatal Intensive Care unit, from January 2015 till May 2016. The study included 80 full term neonates (36 - 42wks) suffering from neonatal hyperbilirubinemia who were divided into four groups: Group (A) which included 20 neonates who received phototherapy with entral feeding only, Group (B) which included 20 neonates who received phototherapy with entral feeding and single oral dose of fenofibrate, Group (C) which included 20 neonates who received phototherapy with entral feeding and daily dose of vit D and Group (D) which included 20 neonates who received phototherapy with entral feeding and daily dose of vit C& vit E.

The mean age of the neonates on admission to our NICU was (3.2±1.3) days in Group (A), in Group (B) was (3.3±1.5) days, in Group C (3.1±1.2) and in Group (D) was (3.1±1.1) with no significant difference between the four groups (table 1).

This is because the typical course of physiologic jaundice peaks around days two to four with or without another cause of jaundice such as RH or ABO incompatibility[9]

Woodgate and Jardine, 2015 explained that Jaundice occurs when there is accumulation of bilirubin in the skin and mucous membranes. In most infants with jaundice there is no underlying disease, and the jaundice is termed physiological. Physiological jaundice typically presents on the second or third day of life and results from the increased production of bilirubin (owing to increased circulating red cell mass and a shortened red cell lifespan) and the decreased excretion of bilirubin (owing to low concentrations of the hepatocyte binding protein, low activity of glucuronosyl transferase, and increased enterohepatic circulation) that normally occur in newborn babies[10].

Conclusion

In conclusion, addition of single oral dose of fenofibrate in jaundiced baby receiving phototherapy in first 24h of treatment can significantly reduce the serum bilirubin levels in term newborns and duration of phototherapy.

Giving daily therapeutic dose of vitamin D in jaundiced baby under phototherapy can significantly reduce the serum levels of indirect bilirubin in term newborns, decrease the duration of phototherapy and act as prophylaxis aganist hazarads of phototherapy.

But honestly we must say that Fenofibrate produces some side effects in adults as gastrointestinal upset and muscle cramps with prolonged use but in neonatal period in a single dose it causes no side effects in our study and up to one month after therapy.

Recommendations

1) The use of a single oral dose of fenofibrate (with a dose 10 mg/kg) with phototherapy accelerates bilirubin conjugation and excretion via induction of glucuronyl transferase activity hence reduces the duration of stay at hospital. Furthermore, fenofibrate decreases the cost of stay, lowers the cost/benefit ratio and at the same time fenofibrate is safe and economic.
2) Although, no side - effects of fenofibrates were observed after a single dose, further studies with a more precise and longer follow up is needed for proving its safety to be used in the treatment of neonatal hyperbilirubinemia.
3) Further studies is needed using active form of vitamin D (1,25-dihydroxy vitamin D3 [1,25(OH)2D3]) during phototherapy of uncomplicated jaundice,as the use of daily dose of vitamin D (400 IU / 24h) (non active) with phototherapy reduces the duration of stay in hospital as vitamin D induces vitamin D receptors (VDR) which in turn act as a receoptor for secondary bile acids. Furthermore,

vitamin D has antineoplastic effects that act as prophylaxsis aganist the possible carcinogenic hazardous of phototherapy.

4) Further studies with a more precise and higher therapeutic doses of vitamin C and E is needed for proving the effect of them to be used in the treatment of neonatal hyperbilirubinemia.

5) Further studies is needed using these agents (fenofibrate, vit D and vit E & C) in treatment of uncomplicated jaundice with lower serum levels of indirect bilirubin (not risk) without phototherapy with follow up of serum indirect bilirubin at shorter intervals each 6-12h to determine its efficacy in dispensing photo-therapy.

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