Iron status of VLBW Preterm Infants Receiving Early Iron Supplementation

Thesis

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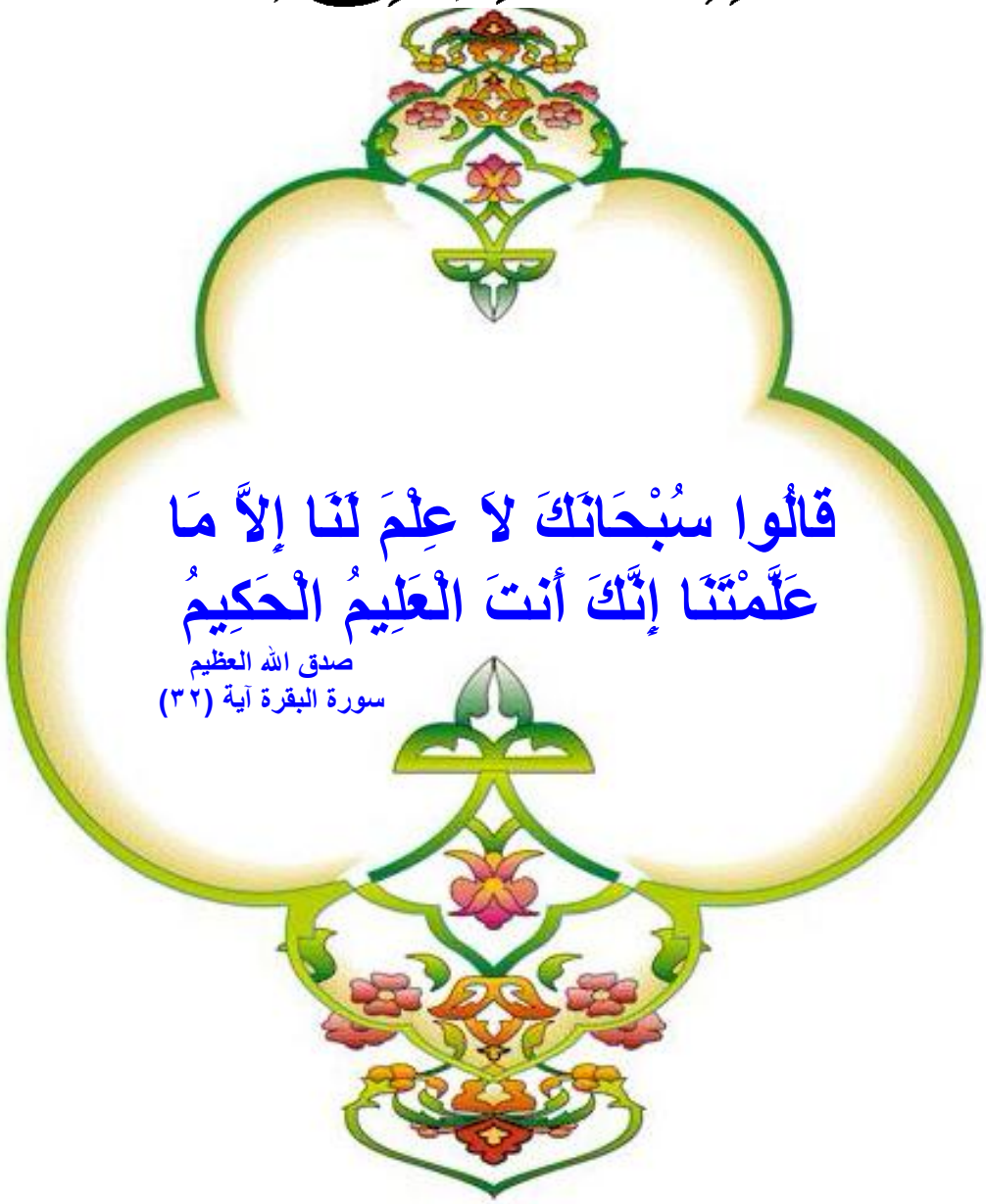
بسم الله الرحمن الرحيم



قالُوا سُبْحَانَكَ لاَ عِلْمَ لَنَا إِلاَّ مَا
عَلَّمْتَنَا إِنَّكَ أَنتَ الْعَلِيمُ الْحَكِيمُ

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Abstract

Reviewing literature, there is a number of limited studies that addressed enteral iron supplementation in treatment of anemia of prematurity. Thus, the present study was designed to evaluate the effect of Iron supplementation at 2 weeks of age on serum iron, ferritin and various hematological parameters in very low birth weight (VLBW) preterm babies.

It was conducted at neonatal intensive care units (NICUs) of Obstetrics and Gynecology Hospital, Cairo University, and Dameitta General hospital during the period from November 2011- till November 2012. It included 30 newborns, very low birth weight (VLBW) preterm infants (birth weight ≤1500 g, <37 weeks gestation) and they were divided randomly into 2 equal groups: ***Group I:*** It included 15 VLBW preterm babies who received enteral iron supplementation at dose of 3mg/kg/day once reaching 90 K calories/ kg/d enterally but not before day 14 of life. ***Group II:*** It included 15 VLBW preterm babies with similar gestational age & clinical conditions, who not supplemented with iron and were considered as control group.

Key words: Iron status - VLBW Preterm Infants Receiving Early Iron Supplementation

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List of abbreviations

AOP	Anemia of prematurity
Cu	Copper
DcytB	Duodenal cytochrome B
DMT1	Divalent metal transporter-1
DNA	Deoxy ribonucleic acid
Epo	Erythropoietin
FLVCR	Feline leukemia virus, subgroup C, receptor
FPN	Ferroportin
Hb	Hemoglobin
HCP-1	Heme carrier protein 1
ID	Iron deficiency
IDA	Iron deficiency anemia
IGF-1/GH	Insulin-like growth factor-1/ growth hormone
IRE	Iron response element
IRP	Iron regulatory protein
ISC	iron-sulphur clusters
Lf	Lactoferrin
MCV	Mean corpuscular volume
NICU	Neonatal intensive care unit
NTBI	Non–transferrin-bound iron
RDA	The recommended daily allowance
STEAP 3	6-transmembrane epithelial antigen of the prostate 3
sTfR	Soluble transferrin receptor
TFRs	Transferrin receptors
TIBC	Total iron-binding capacity
VLBW	Very low birth weight
Zn	Zinc
ZnPP/H	zinc protoporphyrin-to-heme ratio

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Introduction

Iron deficiency (ID) is the most common micronutrient deficiency throughout the world, and infants are at particular risk. Iron plays an important role in the development of the central nervous system and is essential for neural myelination and neurotransmitter function (Berglund et al., 2010).

Iron deficiency anemia (IDA) during infancy is associated with poor neurologic development. Neurodevelopmental deficits related to iron deficiency with or without anemia may not be reversible by iron supplementation and may predispose to long-term cognitive and motor impairment (Arnon et al., 2010).

Depletion of iron stores is usually followed by a decrease in the tissue iron that could induce biochemical defects such as impaired synthesis of DNA and collagen even before any features of microcytic, hypochromic anemia become evident. ID could also affect the growth and function of other organ systems such as skeletal muscle, heart and the gastrointestinal tract (Sankar et al., 2009).

Unlike full-term infants, in whom the condition typically occurs during the second half of infancy, preterm infants are at risk for developing iron deficiency during their first 6 months of life. Gestationally more premature and smaller preterm infants are at greater risk for developing iron deficiency at even earlier age (Rao and Georgieff, 2009).

Preterm infants are commonly supplemented with enteral iron. There

are wide variations in the dose, initiation, duration of supplementation and in the iron compounds used for enteral supplementation (Rao and Georgieff, 2009). The American Academy of Pediatrics recommended an early iron supplementation of 2 to 3 mg/kg/d in preterm infants by 2 months of age. However, even iron administration at such an early age may be associated with iron deficiency (Arnon et al., 2007).

Early oral iron supplementation of 6mg/kg/d from days 7 to 10 of life, (if milk feeds reached 60 ml/kg/d) in infants < 32 weeks gestation was well tolerated and was not associated with morbidities (Rabe et al., 2009). A follow-up study demonstrated a lower incidence of mild motor deficits and a trend toward better cognitive function at 5 years of age in those supplemented from 2 weeks age, suggesting potential long-term benefits with early iron supplementation (Steinmacher et al., 2007).

Aim of the work

To evaluate the effect of Iron supplementation at 2 weeks of age on serum iron, ferritin and various hematological parameters in very low birth weight (VLBW) preterm babies.

Iron Homeostasis in neonates

Iron status of the neonate is a balance between iron accretion during gestation, iron utilization and loss, and iron acquired postnatally, either through enteral or parenteral routes. Thus, maternal and fetal conditions as well as postnatal experiences affect neonatal iron status. Iron is a transition metal that readily converts between the ferrous (+2) and ferric (+3) oxidation states (Cheng and Juul, 2011).

In biochemical systems, iron is often found in the catalytic site of enzymes, where it facilitates redox reactions. Its redox properties provide protein function but can also be dangerous because inappropriate oxidation may cause cellular damage. Free iron in a biologic system can convert between oxidation states, generating free radicals. Polyunsaturated fatty acids, which are found in cell membranes, are especially susceptible to damage by free radicals. To protect the organism, iron is sequestered by proteins throughout absorption, transport, storage, and as it performs its physiologic functions (Hentze et al., 2004).

Figure (1): Iron balance in the neonate is a balance between iron input from prenatal placental transfer; enteral and parenteral iron intake; and transfusions and iron loss via phlebotomy, gastrointestinal loss, and iron use for

Absorption, Transport, and Storage of Iron in Infants

Iron absorption in neonatal period

The uptake of iron by the enterocyte is an important regulatory step in body iron content. Iron can be absorbed into the enterocyte as heme iron or non-heme iron (both ferrous and ferric forms). Heme iron is soluble in the duodenum and is absorbed as an intact metalloprotein via heme carrier protein 1 (HCP-1). Ferrous iron is then released from heme via heme oxygenase (Andrews and Schmidt, 2007).

Unbound iron is absorbed into the enterocyte in the ferrous or ferric form. In the duodenum, non-heme iron is converted to the ferrous (II) form by ascorbic acid and duodenal cytochrome B (DcytB) on the surface of the brush border (McArdle et al., 2008).

Ferrous iron then binds to divalent metal transporter-1 (DMT1) and is transferred into the enterocyte. Expression of DcytB and DMT1 are regulated by the iron content of the enterocyte transcription factors sensitive to hypoxia and intracellular iron concentration (Shah et al., 2009).

Ferric iron (III) binds chelators in the small intestine and is absorbed via a β3 integrin and mobilferrin pathway (Conrad and Umbreit, 2002).

After entry into the enterocyte, ferric iron is reduced by paraferritin and binds mobilferrin. Ferrous iron from all three entry pathways is released into the intracellular iron pool and used for cellular metabolism, stored as ferritin, or transferred out of the enterocyte (McArdle et al., 2008).

Iron is released by ferroportin at the basolateral membrane, where it is oxidized by hephaestin and binds to transferrin for transport. Iron release from the enterocyte into the bloodstream is a tightly regulated process. When the body is iron replete, hepcidin binds ferroportin at the basolateral surface of the enterocyte, inducing internalization and degradation of the protein. This blocks iron release, and iron is incorporated into ferritin in the enterocyte, which is lost when the cells are sloughed. Hepcidin expression is increased in response to iron overload and inflammation and is reduced in response to increased erythropoiesis, hypoxia, and iron deficiency (Andrews and Schmidt, 2007).

Hepcidin production is also reduced during pregnancy, allowing for increased maternal iron absorption (McArdle et al., 2008).

A recent study in mice has demonstrated that H-ferritin, as well as hepcidin, is required for regulation of intestinal iron efflux (Vanoaica et al., 2010).