LPI, transferin saturation, and serum ferritin assay among minimally transfused young thalassemic patients a one year prospective study comparing early and delayed start of low dose deferiprone

Thesis

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List of Abbreviations

BFUe	Blast forming unit erythrocyte
BMP	Bone morphogenic protein
BMPR	Bone morphogenic protein receptor
CFU-e	Colony forming unit committed to erythropoiesis
CT	Computerized tomography
dcytB	Duodenal cytochrome B
DMT1	Divalent metal transporter
EPO	Erythropoietin
ERFE	Erythroferrone
Fe	Iron
FPN1	Ferroportin
GDF11	Growth differentiation factor 11
GDF15	Growth differentiation factor 15
HSP70	Heat shock protein 70
IE	Ineffective erythropoiesis
IRE	Iron responsive element
IRP	Iron regulatory protein

LCI	Labile cellular iron
LIC	Liver iron concentration
LIP	Labile iron pool
LPI	Labile plasma iron
LVEF	Left ventricular ejection fraction
MRI	Magnetic resonance imaging
NTBI	Non transferrin bound iron
ROIs	Reactive oxygen intermediates
ROS	Reactive oxygen species
SMAD	Small mothers against decapentaplegic
TBI	Transferrin bound iron
TfR	Transferrin receptor
TSAT	Transferrin saturation
ZIP14	Zinc import protein

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Abstract

Background: Labile plasma iron (LPI) is considered the major source of iron toxicity; nevertheless LPI control is an essential component of preventive-chelation therapy.

Aim: to detect the time of appearance of LPI in infants with beta thalassemia major in relation to other markers of iron overload and to evaluate the efficacy and safety of the early usage of low dose deferiprone in thalassaemic patients.

Methods: Forty children recently diagnosed with beta thalassemia major; who had begun transfusion without iron chelation therapy; with SF < 400 ng/mL, TSAT < 70% and LPI < 0.2 μM, were enrolled in a prospective randomized study. Patients were followed up every month; when the following criteria SF ≥ 400 ng/ml or transferrin saturation (TSAT) ≥ 70% or LPI ≥ 0.2 μM were met, patients were randomized either to start deferiprone (DFP) at a dose of (50 mg/kg/day) or to be followed with standard observation without chelation (NC).

Results: LPI levels positively correlated with TSAT levels (P<0.001) and age at enrollment (P=0.002), however there was no correlation between LPI and serum ferritin, number of transfusions, amount of transfused RBCs or transfusional iron loading rate. LPI appearance was best predicted by TSAT (AUC=0.975), followed by number of units of transfused RBCs (AUC=0.79), and number of grams of transfused RBC (AUC=0.77), lastly was serum ferritin (AUC=0.66). The cut off value of each parameter was also determined (75% for transferrin saturation, 1090 grams of transfused RBCs, 6 times blood transfusion, and 500 ng/ml for serum ferritin). After randomization all non-chelated patients reached end points prior to completing 12 months

follow-up with a mean duration of 9.82 ± 2.71 and 5.14 ± 2.18 months for chelated and NC respectively.. Serum ferritin was significantly higher in the non-chelated group at 3 month and 6 month visits (P= 0.005, P= 0.007). There was no difference in LPI level or TSAT between the two groups over the post randomization follow up period (P= 0.32, P= 0.27). Both groups had comparable adverse events (P=0.781).

Conclusion: Toxic iron (LPI) might appear early in beta thalassaemic patients at ferritin level <1000ng/dl and fewer number of transfusions (<5 times) with high TSAT. We also demonstrated that the early use of low dose iron chelation therapy significantly decreased the iron overload parameters and was not associated with increased frequency of adverse events.

INTRODUCTION

Regular and frequent red blood cell transfusions have significantly increased the life expectancy of patients with beta thalassemia major (TM). However this leads to excess iron accumulation in many organs leading to progressive organ dysfunction ***(Argyropoulou et al., 2007)***.

Under normal conditions, serum transferrin is 20% to 35% saturated with iron. However, when TSAT is >70%, significant amounts of NTBI appear in plasma ***(Brissot et al., 2012)*** and are deposited in cardiac myocytes, hepatocytes, pituitary cells, and pancreatic cells ***(Breuer et al., 2000).***

There is a fraction of NTBI which is redox-active and is termed labile plasma iron (LPI), the possibly toxic component of NTBI which can be controlled by chelation therapy ***(Brissot.,2012)***; Particularly high levels of NTBI/LPI have been found in beta thalassemia major ***(Koren et al., 2010)***.

Serum ferritin is not always reliable, as it is affected by inflammation and liver damage ***(Argyropoulou et al., 2007)***; Moreover serum ferritin levels often fail to predict impending cardiac iron overload ***(Wood, 2010),*** however its assessment is still economically favorable and may be the only iron overload measure available in some countries ***(Musallam et al., 2013)***.