Comparative Clinical Study to Evaluate the Efficacy and Safety of Oral Liposomal Iron, Oral iron supported Lactoferrin and IV Iron Dextran in Children with Chronic Kidney Disease

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Introduction

Chronic kidney disease (CKD) is a clinical syndrome characterized by a gradual irreversible loss of kidney function that can further progress to end stage renal disease (ESRD) [1].

The diagnosis and staging of CKD is made by estimating glomerular filtration rate (GFR) from a filtration marker serum creatinine [2]. CKD stages are from 1 to 5 depend on decreased GFR [2].

Patients with CKD experience marked alterations in iron balance and distribution, when some cells and tissues are iron deficient and some iron loaded. It leads to dysregulation of physiological crosstalk between iron, oxygen, and erythropoiesis [3, 4]

Anemia is a common comorbidity in children with chronic kidney disease (CKD). This condition is associated with multiple adverse clinical outcomes such as increased risk of cardiovascular disease and decreased quality of life and increased morbidity and mortality [1, 3 &5].

Management of anemia in children with chronic hemodialysis (HD) remains challenging for clinicians [6]. The Kidney Disease Improving Global Outcome (KDIGO) and the Renal Association have described two methods of iron therapy commonly used for ESRD patients undergoing HD: iron repletion (an episodic iron therapy administered when the patient experiences iron deficiency) and maintenance therapy (in which regular iron supplementation at a lower dose is administered). Erythropoiesis-stimulating agents (ESAs) should be coadministered with iron supplementation in the management of anemia in dialysis [7].

Laboratory data of iron deficiency anemia reveals microcytic-hypochromic anemia (reduced Hb, MCV, MCH, elevated red cell distribution width (RDW)) with reduced reticulocyte count. Low ferritin, saturation of transferrin, and high unsaturated serum transferrin are noted. Usually, ferritin is the reference test for assessing the state of iron deposit; however, the lower limits vary according to age and sex. False normal to high levels of ferritin are typical of the inflammatory or infectious state [3].

Another marker of iron metabolism is serum hepcidin, whose levels are significantly reduced in iron deficiency anemia (IDA), elevated in chronic disease anemia and in obesity. Hepcidin is released by hepatocytes. It is the master regulator of systemic iron homeostasis, tightly influences erythrocyte production. High hepcidin levels block intestinal iron absorption and macrophage iron recycling, causing iron restricted erythropoiesis and anemia. Low hepcidin levels favor bone marrow iron supply for hemoglobin synthesis and red blood cells production [8, 9].

During inflammation, macrophages produce high levels of IL-6, the pro-inflammatory cytokine that triggers the expression of hepcidin and decreases the gene expression of ferroportin and therefore decreases intestinal iron absorption. This mechanistic increase in hepcidin levels reduces oral iron absorption in patients with concomitant inflammatory states like CKD, infection and cancer [9, 10].

Growth Differentiation Factor-15 (GDF-15), an anti-inflammatory cytokine is a significant regulator of hepcidin. There is a strong positive correlation between hepcidin and GDF-15 in anemic patients. Anemia induces erythroblasts to secrete GDF-15 which in turn suppresses hepcidin expression and decreases iron stores [11].

According to KIDGO guidelines all CKD pediatric patients with anemia should take oral iron when transferrin saturation (TSAT) is ≤ 20% and ferritin is ≤100 ng/ml (≤100 μg/l) [12]. Pediatric CKD patients on ESA therapy should take oral iron to maintain TSAT >20% and ferritin >100 ng/ml (>100 μg/l) [12].

IV iron maintenance therapy for patients with CKD who receive ESAs and high-dose iron therapy for hemodialysis (HD) increased the risk of infection-related hospitalization, particularly in patients with central venous catheters; however, this was not observed in patients who received oral iron as a maintenance dose [7]. Also, in CKD patients IV iron may increase the numbers of patients who have allergic reactions or hypotension compared with oral iron [13, 14].

The choice of oral iron to use is dictated by goals of therapy, tolerability, convenience, and response to prior therapy. Diminished absorption of iron in the gastrointestinal tract and a high incidence of gastrointestinal adverse effects can reduce the efficacy of oral iron agents. Newer oral agents may help to overcome these limitations and help treat iron deficiency in CKD pediatrics [15].

The most used preparations are oral ferrous sulfate or gluconate due to their high intestinal absorption. However, despite the well-known efficacy, gastrointestinal adverse effects are a major concern of oral ferrous salts, affecting up to 32% of patients. A possible consequence is a low acceptability, scarce adherence to therapy and continuation of IDA [3].

Liposomal iron surrounds the ferric pyrophosphate core with a phospholipid bilayer [3, 10] .This allows for iron to bypass the gastrointestinal tract and be taken up by microfold cells through the lymphatic system, thus avoiding the down-regulating effects of hepcidin and minimizing potential side effects [3, 9].

Lactoferrin (LF) is a non-haem iron binding protein that is structurally and chemically similar to serum transferrin, whose function is to transport iron in blood serum [16]. LF possesses multiple pharmacological properties such as anti-inflammatory, antioxidant and antibacterial [17]. LF contributes to the immune system of the kidney through iron metabolism. It can reduce the damage of excessive inflammatory responses by sequestering free iron and directing reactive oxygen species ROS [18].

Aim

This study aims to investigate the efficacy, tolerability and safety of oral liposomal iron, oral iron supported lactoferrin and IV iron dextran in CKD induced anemia in pediatric.

Patients and methods

Study design

This is a randomized, parallel study that will be conducted on pediatric patients with CKD.

Ethical approval

The study will be conducted following the ethical standards of Helsinki declaration in 1964 and its later amendments. The study will be approved by The Research Ethics Committee of Menoufia University and will be registered on Clinical Trials.gov. All participants will be informed about the benefits and risks of the study. Any unexpected risks that will appear during the course of the research will be clarified to the participant and to be respected and be confidential. A written informed consent will be obtained from all patients or their caregivers. The study will be conducted between December2022 - December2024.

Patients

The study will be conducted on 90 pediatric patients with CKD who will be divided into 3 groups:

Group l: 30 pediatric patients who will receive oral liposomal iron 30 mg/day for 12 weeks.

Group 2: 30 pediatric patients who will receive oral iron supported lactoferrin iron 1 mg+ lactoferrin 100 mg/day for 12 weeks.

Group 3: 30 pediatric patients who will receive IV iron dextran 50 mg/3 times weekly for 12 weeks.

Inclusion Criteria:

A) Pediatrics ≤18 year old male and female patients.

B) Pediatrics with CKD stages 3-5.

Exclusion Criteria:

A) CKD patients' ≥18 year old.
B) Active bleeding
C) Malignancy
D) Anemia due to any disease other than CKD
E) Blood Transfusions

Measurement:

All patients will be submitted to the following analysis at the baseline and 12 weeks after the assigned treatment:

A) History:

1- Demographic data.
2- Clinical history.
3- Medication history.

B) Examination:

Anthropometric measures (weight, height) with subsequent calculation of BMI (weight in kilograms divided by height in meters squared).

C) Laboratory measurements:

1- Hb
2- RBCs
3- WBCs
4- Platelets
5- Hematocrit
6- MCV
7- MCH
8- RDW
9- Serum Creatinine

D) Biological biomarkers and clinical assessments:

1- IL-6: will be assessed by ELISA
2- Hepcidin : will be assessed by ELISA
3- GDF-15: will be assessed by ELISA
4- Serum Ferritin: will be assessed by colorimetric method
5- Serum Iron: will be assessed by colorimetric method
6- TIBC: will be assessed by colorimetric method

E) Calculated parameters

1- TSAT calculation
2- eGFR calculation using Schwartz Equation.

F) Assessment of participant adherence:

During the study duration, the drug and drug tolerability will be provided weekly, and the participant's adherence will be assessed through the medication refilling rate. Participants will be followed up by telephone calls and hospital visits to assess their adherence with caregivers and report any drug-related adverse effects using an adverse effect questionnaire. Patients will be considered non-adherent and excluded from the study

Primary Outcome

The primary clinical outcome is the increase in the amount of oxygen that patients' blood can carry which will be assessed in the 3 arms of the study using measuring red blood cell count and hemoglobin level.

Secondary Outcome

The secondary outcome is the changes in serum levels of biological biomarkers.

Sample size calculation

The sample size was calculated depending up-on a previous randomized (single-blind) non-inferiority clinical trial conducted on 61 patients to study the effectiveness of liposomal iron in pediatric patients in hemodialysis (Flores Pacara, 2022) [19]. In this context, the initial sample size of 61 patients will be sufficient to provide a good power to detect the effect. Assuming that, the attrition rate is 10%, the initial sample size will be 67 patients in the study.
So, 90 patients will be enrolled in our study divided into 3 groups 30 patients will be in each group.

Statistical Analysis

- The collected data will be tabulated using Microsoft® Office Excel, 2019 (Microsoft Corporation).
- The statistical analysis will be carried out using IBM-SPSS statistical package version 26.0 (IBM corporation software group, USA).
- Data will be tested for normality using Shapiro-Wilk test or Kolmogorov-Smimov test.
- Paired student's t-test or Mann Whitney U test to compare the means within the same group and to compare the means between groups.
- Categorical data will be analyzed using Chi-Square test.
- One way analysis of variance (ANOVA) test followed by Post hoc or Tukeys test or Kruskal–Wallis test followed by Friedman test will be used to assess any significant difference between groups before and after treatment.
- Fisher's exact test will be used to analyses the reported adverse effects.
- Correlation between variables will be assessed using Pearson or Spearman correlation coefficient which appropriate.
- Data will be expressed as mean ± standard deviation (SD), medians, range, number and percent as appropriate.
- The significance level will be set as $p \leq 0.05$

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