Effectiveness of Injectable Iron in the Management of Severe Iron Deficiency in Children in Ouagadougou

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Abstract: Background: Iron deficiency anemia affects 90% of children in Burkina Faso. These studies on the effectiveness of injectable iron are rare in low-income countries with high infant and child mortality related to anemia.

Methods: This has been an observational study to assess the effectiveness of injectable iron in children under five years old admitted to the pediatric ward of the Yalgado Ouédraogo University Teaching Hospital (YO-UTH), in 2019, in Ouagadougou, Burkina Faso.

Findings: Thirty-five (35) children with severe iron deficiency anemia (average age 2.5 years), 60 % (n=21) of whom had uncompensated anemia and required transfusion, were treated with injectable iron polymaltose hydroxide and followed up for one month. On average, 226.9±45.5mg of iron were injected over an average treatment duration of three days. The mean hemoglobin count increased from 4.7±0.95g/dl at baseline to 9.7±1g/dl (an increase of 4.9g/dl) one month later (p<0.001). The mean corpuscular volume increased from 69±74fl to 81.5±37fl (p<0.001), and that of the ferritinaemia varied from 0.02±0.005µg/ml to 0.83±0.09µg/ml (an increase of 0.81µg/ml, p<0.001) and the mean sieremia increased from 4.8±2.1µmol/l to 40.4±5.5µmol/l. No side effects were noted.

Conclusion: By avoiding transfusion in most patients, the use of injectable iron in proven and severe iron deficiency anemia could be a solution in case of blood deficit.

Keywords: Anemia, iron deficiency, child, iron, injectable, Burkina Faso.

INTRODUCTION

The World Health Organization (WHO) defines anemia as a decrease in hemoglobin levels below two standard deviations from the norm [1]. It affects 1.62 billion people worldwide, 47.8% of whom are children under five years old [1]. Africa is the most affected continent, with a prevalence of 67.6% of children under five in sub-Saharan Africa [2]. In West Africa, Burkina Faso has the highest prevalence of 88%, including 11% of severe anemia cases [2,3].

More than half of anemia cases are due to iron deficiency [1,4,5]. Severe or uncompensated anemia is a life-threatening condition and requires a blood transfusion. A quarter of the labile blood products (LBP) collected in 2018 in Burkina Faso were administered to children under five years. Yet the satisfaction rate of requests for LBP in 2018 was only 77.71% [6]. The lack of LBP significantly contributes to an increased mortality rate in pediatrics [7], hence the need to find an alternative management approach.

The treatment of iron deficiency anemia with oral iron lasts 6 months and cannot be appropriate for the treatment of certain cases of severe anemia [5,8].

Several studies among pregnant women, preterm infants, and hemodialysis patients have shown an increase in hemoglobin levels twice as fast with injectable iron as with oral iron [9,10]. No such study has been carried out in the context of the high need for labile blood products due to malaria. Therefore, this study aimed to assess the effectiveness of injectable iron in managing severe iron deficiency anemia in children aged zero to five years admitted at the Yalgado Ouédraogo University Teaching Hospital (YO-UTH), Ouagadougou, Burkina Faso.

PATIENTS AND METHOD

Study Design and Participants

This prospective cohort study was conducted between August 1 and October 30, 2018, in the Department of Pediatrics at YO, Ouagadougou, Burkina Faso. The study included children under five years old with severe anemia (hemoglobin level <7g/dl) and iron deficiency with no signs of decompensation. Those with signs of decompensation were included if there was no blood available within 24 hours of hospitalization for transfusion. Iron deficiency anemia was diagnosed on the basis of Hypochromic microcytic anemia, mean corpuscular volume (MCV) < 70 fl (child before 2 years); MCV < 73 fl (between 2 and 5 years and ferritinaemia < 30 µg/l [11-14].
Newborns aged 0 to 28 days and major sickle cell patients (SS and SC) were excluded from the study. Hemoglobin electrophoresis was systematically performed before inclusion, severe emaciation, and renal or hepatic failure.

**Treatment**

All participants were treated with intramuscular injectable iron polymaltose hydroxide (HEMAFER®). The treatment target was an increase of 1.5g/dl of the hemoglobin level. HEMAFER® was presented as 2 ml of 100 mg of iron. The treatment protocol was[15]:

Quantity required = weight x (Anticipated hemoglobin level – the child hemoglobin level) x 2.4 + 15 mg/kg

The maximum daily doses are:

- 0-5kg: 0.5ml = ¼ ampoule (25 mg)
- 5-10kg: 1ml = ½ ampoule (50 mg)
- 10-30kg: 2ml = 1 ampoule (100 mg)
- 30kg or more: 4ml = 2 ampoules (200 mg)

The treatment was administered only by intramuscular route by the department staff (doctors or nurses). The needle used to take the product is changed before injection to avoid staining the injection site. The pain is managed by prior explanation, reassuring, or breastfeeding the child as applicable.

The duration of the treatment varied between two and four days, depending on the quantity of iron required. After administration of injectable iron, patients were monitored every 15 minutes for two hours, then every eight hours for 24 hours, then every 12 hours until the end of treatment. The monitoring consisted in checking the general condition, the Blantyre or Glasgow score, the mucosal staining, signs of respiratory distress, the vital signs (heart rate, respiratory rate, pulse, blood pressure, and temperature), the side effects (inflammation or pigmentation of the injection site, signs of hypersensitivity such as: chills, fever, diffuse pain, sweats, urticaria, edema, hypotension).

Resuscitation equipment (aspirator, nasogastric tubes, gelofusine, adrenaline, ventilation bag and mask, and oxygen) was made available in the monitoring room in case of emergency.

A rapid increase was expected in ferritinemia at the beginning of treatment, with a decreasing trend towards the end of the follow-up. A rapid increase in sideremia at the end of the treatment with relative stability during the follow-up and a slow and progressive increase in erythrocyte markers during the follow-up.

**Assessment of the Treatment Efficacy**

The treatment was deemed effective if it induced an increase in baseline hemoglobin level by 0.5g/dl at D3, 1g/dl at D7, 1.25g/dl at D15, and 1.5g/dl at M1, and in ferritin level by 0.350µg/ml at D3; 0.4µg/ml from D7 to D15 then 0.35µg/ml at D30.

The safety criteria were the absence of major side effects or an alteration of renal and hepatic function, which would be noticed through an increase of 50% or more of the initial value of creatinine and transaminases.

**Follow Up**

Each patient was followed up clinically every day during the hospitalization and then at D3; D7; D15; D30.

A pharmacovigilance form was established to report adverse effects. The hemoglobin level was measured daily during the treatment using a Hemocue

The study assessed the effectiveness of the treatment using hemoglobin level, corpuscular mean volume, ferritinemia, and sideremia before and after treatment. All children were followed for one month with visits on Day 3, Day 7, Day 15, and Day 30. The checkups performed at each visit are shown in Figure 1.

**Sampling**

The minimum required sample size was estimated at 16 patients according to the following formula:

$$N = \frac{4Z_{\alpha/2}^2}{\frac{W^2}{\delta^2}}$$

[16] with $Z_{\alpha}= 1.96$ and $\alpha = 0.05$. The value of 1.5 was taken as our standard deviation ($S$). We set 1.5g/dl as our desired hemoglobin change ($W$). To increase our statistical power, we doubled the sample size.

**Data Analysis**

Paired Student tests were used to compare the means of hemoglobin level, corpuscular mean volume,
ferritinemia, and sideremia before and after treatment, with a p-value of less than 0.05 as a significance level.

RESULTS

Sample Characteristics at Inclusion

This study covered 35 patients, mainly female, with a sex ratio of 0.75. The average age and weight were 30.8 (± 11.8) months and 11.4 (±1.74) kg, respectively. Further socio-demographic characteristics are provided in Table 1.

The biological characteristics are presented in Table 2 below.

Table 1: Socio-Demographic Characteristics

| Characteristics (n= 35)          | Number | Percentage (%) |
|---------------------------------|--------|----------------|
| Place of residence, Rural       | 20     | 57.14          |
| Socio-economic level, Low       | 25     | 71.4           |
| Underweight                     | 18     | 51.4           |
| Malaria                         | 35     | 100            |
| Decompensated anemia,           | 21     | 60             |

Table 2: Patients’ Biological Characteristics at Inclusion

| Characteristics (n= 35)                        | Value                               |
|-----------------------------------------------|-------------------------------------|
| Initial mean hemoglobin (standard deviation)  | 4.7 (± 0.95) g/dl                   |
| Initial mean corpuscular volume (standard deviation) | 66.7 (±4.7) fl                      |
| Initial average serum ferritin (standard deviation) | 0.02 (±0.004) µg/ml                |
| Initial average sideremia (standard deviation) | 4.8 (± 2.1) µmol/l                  |

Progression under Treatment with Injectable Iron

In total, the participants received between 150 and 315 mg of injectable iron with an average of 226.9±45.5mg. The daily dose of iron received ranged from 25 to 100mg with an average of 80±26.9mg for a treatment duration ranging from 2 to 4 days with an average of 3 days.

In addition to the treatment, all patients were treated for malaria (injectable artesunate for 3 days followed by an oral combination of artemether + lumefantrine).

After the treatment, the average time of disappearance of clinical signs of severe anemia was
4±0.5 days for neurological signs, 6.3±0.9 days for cardiovascular signs, and 15 days for conjunctival and palmar/plantar recoloration.

The evolution of erythrocyte indices and serum markers is shown in Figure 2.

**Evolution of Erythrocyte Indices and Serum Markers of Martial Deficiency during Treatment**

Data in Table 3 show the statistical comparisons of the average of erythrocyte indices and serum markers on days 3, 7, 15, and 30 versus day 1 (at inclusion). Overall, there was a significant increase in the level of all markers starting from day 3 after treatment, except for hemoglobin, which improved from day 7.

**Clinical and Biological Tolerance of Injectable Iron**

No side-effect was reported during follow-up; creatinine, urea, transaminases, and blood glucose were normal during follow-up. Table 4 below presents the changes in their average.

![Figure 2: Evolution of serum markers and erythrocyte indices.](image)

**Table 3: Comparison of Changes in Average Erythrocyte Indices and Serum Markers**

|          | Day 1  | Day 3  | Diff* | p    | Day 7  | Diff   | p    | Day 15 | Diff   | p    | Day 30 | Diff   | p    |
|----------|--------|--------|-------|------|--------|--------|------|--------|--------|------|--------|--------|------|
| Mean Hb(g/dl) | 4.7    | 4.5    | -0.05 | <0.05| 6      | +1.33  | <0.001| 8.3    | +3.5   | <0.001| 9.7    | +4.9   | <0.001|
| Mean MCV(fl)  | 66.7   | 66.94  | +0.9  | <0.001| 72.3  | +5.6   | <0.001| 73     | +11.05 | <0.001| 81.5   | +15    | <0.001|
| Mean Ferrit(µg/ml) | 0.02  | 0.79   | +0.77 | <0.001| 0.83  | +0.83  | <0.001| 0.82   | +0.80  | <0.001| 0.83   | +0.81  | <0.001|
| Mean Sider(µmol/l) | 4.8   | 42.07  | +37.24| <0.001| 42.2  | +37.3  | <0.001| 41.88  | +37    | <0.001| 40.4   | +35.63 | <0.001|

*Mean day (3,7,15,30)-Mean day 1.

**Table 4: Comparison of Changes in the Average of Creatinine, Urea, Transaminases, and Glycemia**

|          | Day 1  | Day 3  | Diff* | p    | Day 7  | Diff   | p    | Day 15 | Diff   | p    | Day 30 | Diff   | p    |
|----------|--------|--------|-------|------|--------|--------|------|--------|--------|------|--------|--------|------|
| creat(µmol/l) | 60.5   | 53.2   | -7    | <0.001| 50    | -9.1   | <0.001| 42.3   | -18.2  | <0.001| 40    | -20.5  | <0.001|
| Mean urea (mmol/l) | 3.9    | 3.3    | -0.6  | <0.001| 2.7   | -1.2   | <0.001| 2.6    | -1.3   | <0.001| 2.7   | -1.2   | <0.001|
| Mean ALAT(U/l)  | 16.4   | 13.3   | -3.1  | <0.001| 10.3  | -6.1   | <0.001| 9.4    | -7     | <0.001| 9.5   | -6.9   | <0.001|
| Mean ASAT(U/l)  | 25.6   | 19.8   | -5.8  | <0.001| 20.9  | -4.7   | <0.001| 17.6   | -8     | <0.001| 15.9  | -9.7   | <0.001|
| Mean Glycemia(mmol/l) | 4.2    | 4.7    | +0.8  | <0.001| 5.1   | +1.4   | <0.001| 4.4    | +0.5   | <0.001| 4.8   | +0.9   | <0.001|
DISCUSSION

The study covered thirty-five patients aged 12 to 59 months with severe iron deficiency anemia with an average hemoglobin level of 4.7±0.95g/dl, and an average baseline serum ferritin and sideremia levels of 0.02±0.004µg/ml and 4.8±2.1µmoles/l respectively. They were treated with 226.9±45.5mg of injectable iron polymaltose for three days on average and followed up for one month. At D30, the mean hemoglobin level was 9.7±1g/dl; the average serum ferritin and sideremia were 0.83±0.09µg/ml and 40.4±5.5µmol/l, respectively.

Patients’ Characteristics at Baseline

The average age of our patients was 30.8±11.8 months. This age is the most common for nutritional deficiencies and malaria [3].

The majority (51.4%) of our patients were underweight. This is because a martial deficiency in our context is mainly due to insufficient intake. In addition, 71.4% of our patients were from families with a low socio-economic level. According to the FAO, the lower the socio-economic level, the higher the consumption of iron-deficient foods [17].

All patients had malaria because, on the one hand, the study was conducted in a hospital setting during the endemic period of malaria and in a country where the prevalence of malaria is very high, i.e., 17% in children aged 6 to 59 months according to the 2018 Burkina Faso Malaria Indicator Survey [18]. On the other hand, malaria sometimes occurs in patients already weakened by martial deficiency worsening anemia.

The initial hemoglobin level of 4.7±0.95g/dl was lower than those of other authors, which ranged from 6.3g/dl to 7.7g/dl in Surico in Italy[19], Kriplanie in India [20], Mantadakis in Texas [21], Hussain in Pakistan [22].

Effectiveness of Treatment with Injectable Iron

Evolution of the Hemoglobin Level

From D7 to D30, there was a statistically significant increase in the average hemoglobin level of 4.9g/dl (p=0.000). This increase was greater at D30. This result is roughly equal to that of Mantadakis et al. in Texas, who found an increase of 4.8g/dl [21]. Hussain et al. gained 5.3g/dl [22]. These results provide evidence of the effectiveness of injectable iron.

Evolution of Ferritinemia

A rapid increase was recorded in average ferritin levels at the start of treatment. It increased from 0.02µg/ml at D0 to 0.79± 0.11µg/ml, i.e. a rapid increase of 0.77µg/ml (p<0.001) at D3. This was followed by relative stability between D7 and D15, followed by a downward trend from D30.

This rapid increase just at the end of the treatment is in line with the data in the literature about treatment with injectable iron. Indeed, in the treatment with injectable iron, the ferritinemia increases rapidly and normalizes before the erythrocyte parameters because the body receives a significant quantity of iron and stores it [23,24]. The study found a downward trend in ferritin levels at D30. This is because the amount of iron we administered was sufficient to increase the hemoglobin level by 1.5g/dl. This goal was achieved, and we see a continual increase in hemoglobin. The organism, therefore, draws again on its iron reserves (ferritin) to ensure the needs of erythropoiesis.

Evolution of Sideremia

The evolution of sideremia in our patients followed the same trends as that of ferritinemia. A high increase at the beginning (+37.24µmol/ml with p<0.001), followed by a downward trend. These data are in line with those in the literature regarding injectable iron. The high serum iron quickly stabilizes after being used for erythropoiesis and spared as ferritin [22,25].

Safety of the Treatment

No side effects were recorded in the short term, and the parameters of renal and hepatic functions remained normal from beginning to end. This good tolerance of iron polymaltose has also been noted by Surico et al. [19], Newnhom et al. [26], and Litton et al. [24]. However, we cannot comment on the medium- and long-term effects because our post-treatment monitoring was only one month.

Limits and Constraints

• The unavailability of an emergency martial assessment caused a delay in the diagnosis of martial deficiency and in the initiation of treatment.
• The fact that all the patients in the study were malaria positive may have been a bias in the clinical assessment of the severity of the anemia and the efficacy of iron at the beginning of the treatment. The short period of our monitoring did
not allow us to know the ultimate evolution of erythrocyte indices and serum markers and as well as the safety of injectable iron in the long term.

CONCLUSION

Injectable iron is not part of current therapeutic practices in pediatrics. However, when it is used at an early stage of severe anemia due to martial deficiency could help correct the martial deficiency and reduce the need for blood transfusion.

ETHICAL CONSIDERATION

Written and signed consent was required from one of the patients' parents.

CONFLICT OF INTEREST

The Uni-Pharma laboratory provided funding for the following aspects of the study: the performance of the various tests for diagnosis and follow-up, injectable iron for treatment, and HemoCue for measuring the daily hemoglobin level. However, they had no role in the conceptualization, the analysis, and the reporting of the study. Uni-Pharma laboratory was not involved in any aspect of the study.

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