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Original Scientific Paper

TRANSIENT HYPOPHOSPHATEMIA AS POSSIBLE ADVERSE OUTCOME AFTER IRON DEFICIENCY ANEMIA TREATMENT WITH FERRIC CARBOXYMALTOSE – SINGLE CENTER EXPERIENCE

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SUMMARY – The aim of this study was to determine the frequency of hypophosphatemia in female patients with iron deficiency anemia (IDA) treated parenterally with ferric carboxymaltose (FCM). Thirty-two female patients examined for IDA at the Hematology and Oncology Department of one General Hospital were included in the study. The inclusion criteria were hemoglobin <110 g/L, transferrin saturation <50%, ferritin <30 ng/mL, and ineffective oral iron therapy. The hemoglobin values were significantly increased 6 weeks after therapy in comparison with initial values. The onset of the asymptomatic hypophosphatemia was observed in 17 of 32 patients two weeks after the FCM therapy. Only one of 32 patients had severe asymptomatic hypophosphatemia (serum phosphate <0.3 mmol/L). Prolonged hypophosphatemia (6 weeks after FCM therapy) was observed in five of 32 patients, of which only one patient had initial hypophosphatemia. The difference between the phosphate values measured two weeks after the FCM therapy and the phosphate values at the first and last follow-up was statistically significant. Serum phosphate values should be routinely measured before and after parenteral FCM therapy.

Keywords: *Ferric carboxymaltose; Hypophosphatemia; Iron deficiency anemia*

Introduction

Ferric carboxymaltose (FCM) is an iron formulation for parenteral treatment of iron deficiency anemia (IDA) (1). A possible adverse effect of parenteral iron therapy is a transient hypophosphatemia secondary to increased phosphaturia triggered by an increase in fibroblast growth factor 23 levels (FGF23) (2–4).

Hypophosphatemia symptoms are nonspecific and include fatigue, proximal muscle weakness, and bone pain. Patients receiving frequent parenteral iron therapy are at risk of osteomalacia due to prolonged hypophosphatemia. A clinician prescribing parenteral iron therapy should consider the risk of hypophosphatemia to prevent possible complications. Depending on the grade of hypophosphatemia, most patients feel better after oral or venous phosphate replacement.

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The aim of this study was to assess the frequency of hypophosphatemia as a possible adverse effect after FCM therapy in female patients with IDA.

Patients and methods

Thirty-two female patients were examined at the Hematology and Oncology Department of one General Hospital and included in the study. The etiology of sideropenic anemia was menstrual bleeding or bleeding from the digestive tract with excluded malignant disease. The inclusion criteria were IDA with hemoglobin (Hb) <110 g/L, transferrin saturation (TSAT) <50%, ferritin <30 ng/mL, and ineffective oral iron therapy.

This prospective study was conducted between February 1 and June 1, 2017. All procedures were performed in accordance with the 1983 revision of the Declaration of Helsinki. As FCM is standard treatment for sideropenic anemia, patients were not required to sign informed consent.

The measured biochemical parameters included hemoglobin (Hb), iron (Fe), unsaturated iron binding capacity (UIBC), total iron binding capacity (TIBC), ferritin, serum phosphate, vitamin D, serum calcium, and parathyroid hormone (PTH). Biochemical testing was performed before FCM therapy (initial examination) and then during follow-up at two and six weeks after FCM therapy. The patients received FCM at a dose of 1000 mg. Four patients did not return to all follow-up examinations and thus did not complete the study.

Statistical analysis

Data are expressed as mean values appropriate to the type of distribution. Normality of the distribution was determined by Shapiro Wilk test. Quantitative variables were compared using t-test or Wilcoxon test for dependent samples. The significance level was set at $p<0.05$. Statistical analysis was performed with MedCalc Statistical Software version 19.2.1 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2020).

Results

The mean (±standard deviation, SD) age of patients was 55.6±16.4 years. All mean values of biochemical parameters measured before and after FCM therapy are shown in Table 1.

The mean difference between Hb values measured before FCM therapy and six weeks after FCM therapy

*Table 1. Biochemical parameters at initial measurement, 2 and 6 weeks after ferric carboxymaltose therapy, reported as mean values (arithmetic mean and standard deviation, or median with interquartile range)**

Parameter	Initial values (n=28)	Week 2 values (n=28)	Week 6 values (n=28)
Hb (g/L)	87±10.8	111.5 (83-149)	126.6±11.4
Fe (μmol/L)	2.6 (0.9-12.5)	13.6±4.2	12.8±4.9
UIBC (μmol/L)	70.5±9.8	43±7.6	43±8.4
TSAT (%)	4 (1-21)	25 (15-66)	23.5±8.9
Ferritin (ng/L)	5.8 (2.4-221)	200 (18-1538)	41 (14-553)
Serum phosphate (mmol/L)	0.96±0.19	0.67±0.24	0.98±0.22
PTH (pg/mL)	54.8 (6-122)	77±30.7	60±29
Serum Ca (mmol/L)	2.24±0.07	2.24 (1.9-2.43)	2.29 (0.5-2.52)
Vitamin D (μg/L)	31.4 (7.5-175)	31.4 (7.5-87.4)	33.6 (7.5-111)

Abbreviations: Hb = hemoglobin, Fe = iron; UIBC = unsaturated iron binding capacity; TSAT = transferrin saturation; P =phosphate; PTH = parathyroid hormone; Ca = calcium

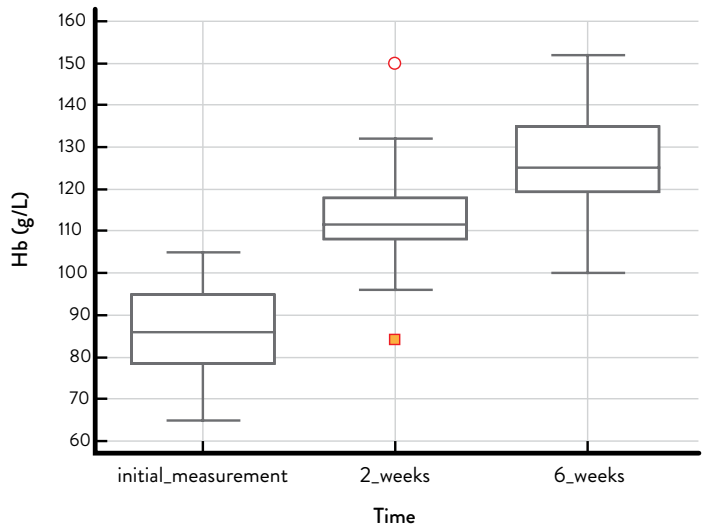

Fig. 1. The comparison of the initial hemoglobin values and hemoglobin values measured 2 and 6 weeks after ferric carboxymaltose therapy.

was 38.5 g/L (95% confidence interval (CI): 32.5–44.5 g/L, paired samples t-test, p<0.001; Fig. 1).

At the initial measurement before FCM therapy, Fe values were below 8 µmol/L in 93% of the patients (reference range: 8-30 µmol/L). The Hodges-Lehmann median difference between Fe values measured before and six weeks after FCM therapy was 9.5 µmol/L (95% CI: 7.9–10.85 µmol/L, Wilcoxon test for paired samples, p<0.001).

UIBC values before FCM therapy were above 59 µmol/L (reference range: 26-59 µmol/L) in 93% of the patients. At the final examination six weeks after FCM therapy, UIBC values were within the reference interval in all patients.

Before FCM therapy, TSAT was lower than 20% in almost all patients. The Hodges-Lehman median difference between TSAT values measured before and six weeks after FCM therapy was 19% (95% CI: 16%-22%, Wilcoxon test paired samples, p<0.001; Fig. 2).

Before FCM therapy, 11 patients had ferritin values below the reference range (4.63-204 ng/mL). Ferritin values measured six weeks after FCM therapy were within the reference range in 96.3% of patients. The Hodges-Lehman median difference between ferritin values measured before and six weeks after FCM therapy was 52.7 ng/mL (95% CI: 30.8-93.9 ng/mL, Wilcoxon test for dependent samples, p<0.001).

Initially measured PTH values were greater than 65 pg/mL in 7 patients (reference interval: 16-65 pg/mL). The difference between the PTH values measured before and two weeks after FCM therapy was 13.8 pg/mL (95% CI: 5.53-25.98 pg/mL, Wilcoxon paired-samples test, p=0.002). The Hodges-Lehmann median difference between PTH values measured two and six weeks after FCM therapy was -16.5 pg/

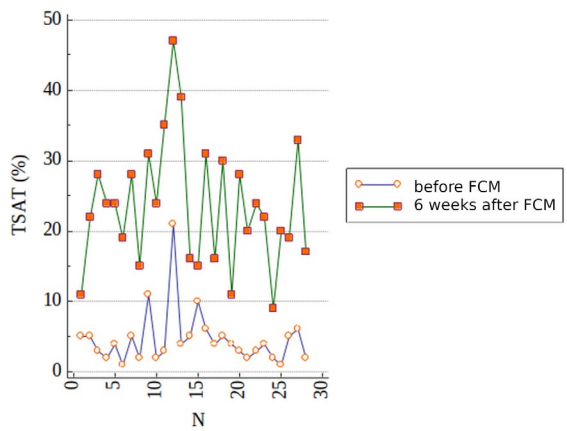

Fig. 2. Transferrin saturation (TSAT) values for each patient before and 6 weeks after ferric carboxymaltose (FCM) therapy.

mL (95% CI: -27.78 to -6.06 pg/mL, Wilcoxon paired-samples test, p=0.01).

Before the FCM therapy, four (14%) patients had moderate hypophosphatemia (serum phosphate: 0.3-0.8 mmol/L). Of the four patients with pre-existing hypophosphatemia, two had an increase in serum phosphate (0.52-0.66 mmol/L and 0.64-0.73 mmol/L) two weeks after FCM. The third patient had an asymptomatic decrease in serum phosphorus (0.58-0.41 mmol/L), with increasing values of serum phosphate to 0.78 mmol/L at the last follow-up examination. The fourth patient had normal phosphate values in the same period (0.66-1.04 mmol/L).

The new-onset of hypophosphatemia was observed at follow-up examination two weeks after FCM therapy in 17 (61%) patients. Newly developed severe hypophosphatemia (serum phosphate <0.3 mmol/L) was observed in only one (3.7%) patient.

The mean difference between serum phosphate values measured before and two weeks after FCM therapy was -0.29 mmol/L (95% CI: -0.4 to -0.18 mmol/L, paired samples t-test, p<0.001). The comparison of serum phosphate values measured before and two weeks after FCM therapy for each patient is shown in Fig. 3.

Prolonged hypophosphatemia was found in 5 (18.5%) patients at the follow-up examination six weeks after FCM therapy. One of these patients had hypophosphatemia at the initial evaluation, i.e. before FCM therapy. All patients were asymptomatic. The mean difference between serum phosphate values measured two and six weeks after FCM therapy was 0.3 mmol/L (95% CI: 0.2-0.4 mmol/L, paired samples t-test, p<0.001; Fig. 4).

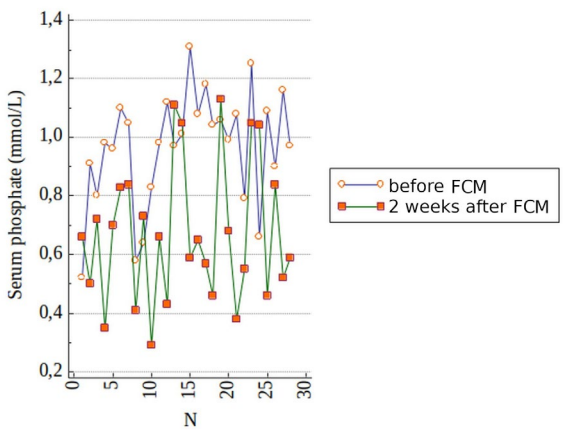

Fig. 3. The comparison of the serum phosphate values for each patient before and 2 weeks after ferric carboxymaltose (FCM) therapy.

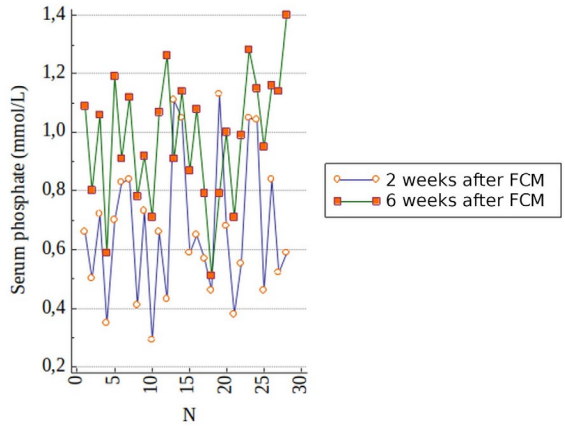

Fig. 4. The comparison of serum phosphate values for each patient measured 2 and 6 weeks after ferric car boxymaltose (FCM) therapy.

Discussion

Sideropenic anemia is common in women because of menstrual bleeding. According to some authors, as many as 30% of women of childbearing age have sideropenic anemia (5).

In the available literature, most research on the side effects of parenteral iron in the treatment of IDA has been performed in female subjects, so it is difficult to discern whether women are more prone to hypophosphatemia in comparison with men. Detlie et al (6) conducted a prospective observational study of the incidence of hypophosphatemia after administration of FCM and iron isomaltoside to 130 patients (55% were women) with IDA within IBD. The incidence of hypophosphatemia 2 weeks after FCM administration was significantly higher than in the group receiving iron isomaltoside (56.7% vs 5.7%). The authors did not find any association of hypophosphatemia with gender, age, or diagnosis (6). Although patients with IBD may have deficiency and insufficiency of vitamin D, which is an important part of phosphate homeostasis,

because of the disease itself or inadequate intake of the vitamin (7).

The onset of transient hypophosphatemia as adverse effect of parenteral iron therapy is documented in the literature but the clinical meaning still is not investigated. Several studies compared two iron formulations for parenteral therapy of IDA and described a higher incidence of the hypophosphatemia after FCM administration (8–11). In one review article, the reported rate of hypophosphatemia after FCM ranged from 0.0% to 92.1% (12).

FGF23 has been associated with familial hypophosphatemic osteomalacia (13) and examined for usefulness in assessing acute renal failure (14). FGF23 is produced in bone. It causes increased phosphate excretion by inhibiting Na^+-dependent phosphate cotransporter in the proximal tubules of the kidney (2,15). One of the proposed mechanisms of how FCM affects FGF23 is that FCM inhibits the conversion of FGF23 to an inactive form and thus increases the concentration of biologically active FGF23 (2,15).

The readers may be wondering why we only examined side effects after applying FCM therapy. When we planned the research, two groups of subjects with sideropenic anemia were formed – one group with malignant disease and the other group without malignant disease. Our goal was to see the effect of parenteral iron on the correction of hemoglobin values and possible side effects of the drug in both groups. Iron isomaltoside was administered to the malignant group and FCM to the non-malignant group. In the group receiving FCM, we noticed the significant incidence of onset asymptomatic hypophosphatemia which we found valuable to report. Both groups achieved a satisfactory increase in hemoglobin values, but our mistake was that we did not administer the same iron preparation to both groups, so these findings could not be compared.

Four of our patients already had moderate hypophosphatemia before FCM therapy. They were asymptomatic and had no known disease that could affect phosphate metabolism. One of them had a lower serum phosphate level with normal vitamin D, PTH, and serum calcium. Another patient had PTH 108 ng/L, serum calcium 2.03 mmol/L, and vitamin D in the reference range. The third patient had serum calcium 2.12 mmol/L, and vitamin D and PTH in reference range. The fourth patient had moderate hypophosphatemia with vitamin D above reference range and normal values of PTH and serum calcium.

One of the reasons we decided to report our results was to address the question of whether it is safe to administer FCM to patients with pre-existing hypophosphatemia, as serum phosphate is not routinely measured before or after parenteral iron administration. No clinically significant hypophosphatemia has been reported in previous studies, and its clinical significance has not yet been examined. In our study, the newly developed hypophosphatemia was recorded two weeks after FCM in more than half of our patients, and four patients had pre-existing hypophosphatemia.

Favrat et al (16) conducted a randomized, placebo-controlled, single-blind study of FCM efficiency in the treatment of iron deficiency in premenopausal women with no other chronic medical conditions. At the seventh day after FCM therapy, 86% of FCM-treated patients and 2% of patients in the placebo group had moderate asymptomatic hypophosphatemia (16).

Hardy and Vandemergel (9) reported that 51% of their patients had moderate hypophosphatemia (serum phosphate <0.80 mmol/L) after FCM therapy, and 13% of their patients had severe hypophosphatemia (serum phosphate <0.32 mmol/L), which is more than in our study.

Wolf et al (10) performed a randomized trial of intravenous iron-induced hypophosphatemia in two groups of patients. One group included 1000 patients (77.6% women) who were treated with FCM. Another group consisted of 997 patients (74.5% women) who were treated with ferumoxytol. The etiology of IDA in patients of both groups was abnormal uterine bleeding (24%), gastrointestinal blood loss (28.5% for FCM and 29.8% ferumoxytol), chronic kidney disease (26%), and unknown or other reason (19%). By a multivariate analysis model that included gender, age, race, body weight, cause of IDA, baseline serum phosphate, Hb, Fe, ferritin, and eGFR, FCM treatment versus ferumoxytol was assessed as the most significant risk factor for hypophosphatemia (10). The serum phosphate levels were significantly reduced two weeks after therapy, which is in line with our findings.

Mani et al (17) described a patient with a stable kidney transplant who was diagnosed with severe and symptomatic hypophosphatemia (serum phosphate

0.16 mmol / L) one month after the FCM administration. Tournis et al (18) described the case of the patient with hypophosphatemia, severe bone pain, and fractures after iron substitution in IBD. Several other cases of the severe hypophosphatemia following the FCM therapy have also been reported in the literature (19–25).

The disadvantages of our study were a small sample size and that it included only female participants. Women of childbearing age were selected on the assumption that they had no other comorbidities. Another possible influence on the measured parameters in the study are diet and dietary supplements that have not been recorded and analyzed.

Conclusion

This study included a small group of women and 14% of them had initially moderately low serum phosphate with no symptoms and not known cause. The analysis of parameters related to serum phosphorus balance (PTH, vitamin D and serum calcium) did not show an association of these parameters with hypophosphatemia before or after FCM treatment. The FCM therapy successfully corrected IDA in all patients.

Although FCM is highly effective therapy for IDA and widely used in everyday clinical practice, clinicians should be aware of potential adverse outcomes, such as hypophosphatemia, which was also described after therapy with other types of parenteral iron. However, the incidence of hypophosphatemia seems higher after FCM therapy.

The symptoms of hypophosphatemia are nonspecific and very similar to the symptoms of anemia, so they may be mistakenly attributed to the IDA. The main conclusion of this paper is that serum phosphate values should be routinely measured in the patients receiving FCM therapy to prevent a possible long-term side effect of hypophosphatemia on bone homeostasis.

Future studies should include a larger number of patients, equal numbers of men and women, and equal diagnoses, receiving frequent parenteral iron, to monitor the incidence of hypophosphatemia and its effects on the bone metabolism.

CONFLICT OF INTEREST: The authors declare no conflict of interest.

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Sažetak

PROLAZNA HIPOFOSFATEMIJA KAO MOGUĆI NEŽELJENI ISHOD LIJEČENJA SIDEROPENIČNE ANEMIJE ŽELJEZOVOM KARBOKSIMALTOZOM – UNICENTRIČNO ISPITIVANJE

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Cilj ovog ispitivanja bio je ispitati učestalost hipofosfatemije nakon parenteralnog liječenja primjenom željezove karboskimaltoze u pacijentica sa sideropeničnom anemijom. U ispitivanje su uključene 32 pacijentice pregledane zbog sideropenične anemije na Odjelu za hematologiju i onkologiju jedne Opće bolnice. Kriteriji za uključivanje bili su hemoglobin < 110 g/L, saturacija transferina < 50 %, feritin < 30 ng/mL te neuspješno liječenje oralnim pripravcima željeza. Vrijednosti hemoglobina 6 tjedana nakon terapije bile su statistički značajno više od početnih. Novonastala hipofosfatemija zabilježena je u 17 pacijentica od njih 32 dva tjedna nakon terapije. Teška ali asimptomatska hipofosfatemija (serumski fosfat < 0,3 mmol/L) zabilježena je kod jedne pacijentice. Na zadnjem kontrolnom pregledu (6 tjedana nakon terapije) asimptomatska hipofosfatemija zabilježena je u 5 pacijentica, s time da je jedna pacijentica imala hipofosfatemiju prije terapije. Razlika između vrijednosti serumskih fosfata mjerenih 2 tjedna nakon terapije i vrijednosti mjerenih prije terapije i 6 tjedana nakon terapije statistički je značajna. Preporučuje se rutinski mjeriti vrijednosti serumskog fosfata prije i nakon terapije željezovom karboksimaltozom.

Ključne riječi: *Hipofosfatemija; Sideropenična anemija; Željezova karboksimaltoza*