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Role of Ferric Sodium EDTA Associated with Vitamin C, Folic acid, Copper gluconate, Zinc Gluconate and Selenomethionine Administration in Patients with Secondary Anaemia: Effects on Hemoglobin Value and Cardiovascular Risk

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Abstract

Introduction: Iron-Deficiency anaemia (IDA) has a high impact on the quality of life in old patients when affected by chronic heart failure and/or respiratory diseases. The aim of this study is to investigate the efficacy and safety of Ferric Sodium EDTA in combination with vitamin C, folic acid, copper gluconate, zinc gluconate and selenomethionine (Ferachel forte®) 2 tabs/day for 24 days, in elderly patients with secondary anaemia, analysing cardiovascular risk and quality of life by means of ECG and bioelectrical impedance (BIA) analyses.

Materials and methods: We have enrolled 43 elderly patients, divided in 2 groups: the first one (N=14 patients) treated with oral administration of Ferric Sodium EDTA in combination with vitamin C, folic acid, copper gluconate, zinc gluconate and selenomethionine (Ferachel forte®) 2 tabs/day, containing 60 mg of Fe^{3+}, for 24 days, the second one (N=29 patients) treated with ferrous gluconate 63 mg/day added to saline solution administered using intravenous access during the hospitalization period of 15 ± 5 days. We evaluated laboratory values of red blood cells, hemoglobin (Hb), and iron blood profile. We measured also the ECG signals and the bioelectrical impedance (BIA).

Results: This study showed that oral treatment with Ferric Sodium EDTA combination at the iron dosage of 60 mg (2 tabs/day) is an effective treatment for the improvement of Hb levels and iron blood profile. Intravenous iron supplementation exposes patients to a greater water supply, confirmed by BIA analysis, and give a statistically significant variation of the T-peak-to-T-end index, representing a predictive parameter of arrhythmic risk.

Conclusions: The therapy with Ferric Sodium EDTA, in combination with vitamin C, folic acid, copper gluconate, zinc gluconate and selenomethionine (Ferachel forte®) showed a real superiority and could be a valid alternative to ferrous gluconate intravenous therapy in the treatment of secondary anaemia in elderly patients.

Keywords: Iron-Deficiency Anaemia; Cardiovascular risk; Kidney failure; Ferric sodium EDTA; Elderly; Quality of life

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Introduction

Iron deficiency (ID) is a global problem affecting more than two billion people worldwide. Patients with ID show reduced levels of total body iron, especially iron stores, but maintain unchanged levels of erythroid iron. Following to worsening of ID, Iron-

Deficiency Anaemia (IDA) can occur, showing low levels of iron, associated with the presence of microcytic hypochromic red cells [1]. According to WHO criteria, anaemia is defined as blood hemoglobin (Hb) concentration <13 gr/dL in adult males and Hb concentration <12 gr/dL in non-pregnant adult females [2]. Anemia is a frequent co-morbidity in patients with heart disease, ranging from 10% to 20% of patients with coronary heart disease (CHD) and affecting about one third of patients with congestive heart failure (CHF) [3]. IDA has a high impact on the quality of life in old patients when affected by chronic heart failure and/or respiratory diseases. In such frailty patient, IDA causes a worsening of cardiac function and exercise capacity, together with an increased risk for hospitalization and death. Therefore, anaemia evaluation and follow-up are included in cardiovascular guidelines. Several causes are involved in pathophysiological mechanisms of anaemia and also several classifications of anaemia can be made. All causes of anaemia give impaired hemoglobin levels and red blood cells values. In general anaemia can be due to:

- Hypo-proliferative disorders, including normocytic normochromic anaemia caused by: 1] marrow damage for infiltration or fibrosis or aplasia; 2] iron deficiency, 3] low stimulation for inflammation or metabolic defect or kidney disease,

- Maturation disorders, including micro or macrocytic disorder due to: 1] cytoplasmic defects for iron deficiency or thalassemia or sideroblastic anaemia, 2] nuclear defects for folate deficiency or vitamin B12 deficiency or drug toxicity or refractory anaemia,

- Haemolysis and haemorrhagic problems, including 1] blood loss 2] intravascular haemolysis, 3] metabolic defects, 4] membrane abnormalities, 5] hemoglobinopathies, 6] immune destruction, 7] fragmentation haemolysis [4].

ID is one of the main causes of anaemia, and excluding inherited red cells disorders, such as β-thalassemias, IDA seems to be the main factor involved in the increased years life lived with disability (YLD) observed in all ages and in both sexes. IDA treatment is based on iron supplementation, as oral or intravenous iron administration, depending on Hb levels, the tolerance to oral iron supplementation and the presence of concomitant disease, which might affect iron absorption. Iron administration is associated with improvements of cardiovascular outcomes and quality of life [1-7]. The aim of this study is to investigate the efficacy and safety of Ferric Sodium EDTA in combination with vitamin C, folic acid, copper gluconate, zinc gluconate and selenomethionine (Ferachel forte®) 2 tabs/day for 24 days, in elderly patients with secondary anaemia, analysing cardiovascular risk and quality of life by means of ECG and bioelectrical impedance (BIA) analyses.

Materials and Methods

We have enrolled 43 elderly patients, divided in 2 groups: the first one (N=14 patients) treated with oral administration of Ferric Sodium EDTA in combination with vitamin C, folic acid, copper gluconate, zinc gluconate and selenomethionine (Ferachel forte®) 2 tabs/day, containing 60 mg of Fe^{3+}, for 24 days, the second one (N=29 patients) treated with ferrous gluconate 63 mg/day added to saline solution administered using intravenous access during the hospitalization period of 15 ± 5 days.

Subjects studied

The enrolled patients (age: 78.2 ± 13.1 years) had a recent diagnosis of secondary anaemia due to iron deficiency and low-moderate kidney failure (Mean Creatinine Value: 1.1 ± 0.6 mg/dL in the group treated with oral administration of Ferric Sodium EDTA combination and 1.4 ± 1 mg/dL in the group treated with intravenous administration). We evaluated laboratory values of red blood cells, Hb, and iron blood profile. We estimated the improvement of laboratory values and the adherence to therapy before and post-administration of Ferric Sodium EDTA combination vs. ferrous gluconate therapy. For the ECG signal analysis, we used Cardio CE palm version 2.0 (XAI-Medic) to register standard ECG and beat to beat ECG for Heart Rate Variability (HRV) evaluation. Using a short registration of the electrocardiographic trace the T-peak to T-end index (Tp/Te) and the Qt correct interval (QTc) have been measured [8]. The bioelectrical impedance (BIA) has been analysed with the Bodygram PRO 3.0 (Akern) [9]. We used international scale for Laboratory test (creatinine mg/dL). Statistical analysis is performed using Wilcoxon signed rank test (Z) with Sigmastat v. 3.5 analysis program.

Results

This study showed that oral treatment with Ferric Sodium EDTA, in combination with vitamin C, folic acid, copper gluconate, zinc gluconate and selenomethionine (Ferachel forte®) at the iron dosage of 60 mg (2 tabs/day) is an effective treatment for the improvement of Hb levels and iron blood profile. Results showed increased levels of both Hb and sideraemia, with a similar trend between oral iron supplementation for 24 days and intravenous iron infusion, administrated during hospitalization period (15 ± 5 days). In particular, Hb levels raised from 9.5 ± 1.3 g/dL to 11.7 ± 1.9 g/dL (P=0.001) in the group treated with Ferric Sodium EDTA combination (**Table 1**). The corresponding increase in Hb levels in intravenous iron-treated group was from 8.9 ± 1.5 g/dL to 9.9 ± 1.9 g/dL (P=0.001; Table 2). Similar results were obtained for sideraemia levels: from 19.5 ± 5.6 mcg/dL to 53.8 ± 25.9 mcg/dL (P=0.001; **Table 1**) for oral iron administration group; and from 19.6 ± 12.2 mcg/dL to 37.1 ± 21.9 mcg/dL (P=0.001; **Table 2**) for intravenous therapy

Table 1 Ferric Sodium EDTA in combination with vitamin C, folic acid, copper gluconate, zinc gluconate and selenomethionine (Ferachel forte®) (2 tabs/day, for 24 days); n.a.=Not Available. The data are expressed as value ± DS.

	Control	Effect	P Value
Hb (g/dL)	9.5 ± 1.3	11.7 ± 1.9	0.001
Fe^{++} (mcg/dL)	19.5 ± 5.6	53.8 ± 25.9	0.001
RR (msec)	778.5 ± 179.1	814.5 ± 172.9	0.125
LF (msec)	600.5 ± 626.1	1442.4 ± 3017.3	0.625
HF (msec)	854.9 ± 909.9	2780.1 ± 6137.1	0.688
Tp-e (msec)	96.8 ± 14.9	95.8 ± 12.9	0.844
QTc (msec)	317.3 ± 28.6	318.3 ± 30.6	0.625
Tp-e/QTc	0.304 ± 0.04	0.301 ± 0.04	0.844
Resistance (Ω)	n.a.	n.a.	n.a.
Reactance (Ω)	n.a.	n.a.	n.a.

group. Furtherly, our data showed that oral treatment with Ferric Sodium EDTA combination is well tolerated (**Table 1**). Throughout the study, none adverse events related to iron overload has been reported, neither at liver level neither as hemolysis. Only one patient has referred transient diarrhea solved by reducing the Ferric Sodium EDTA combination dose at 30 mg of Fe^{3+} (1 tab/day). The HRV analysis did not show any statistical difference in the values due to the therapy but analyzing electrocardiographic signals our data showed a statistically significant variation of the T-peak-to-T-end index in patients with intravenous iron supplementation (**Table 2 and Figure 1**). In these patients, T-peak-to-T-end index was statistically higher than in the patients in therapy with oral iron administration. This fact represents a predictive parameter of arrhythmic risk. Our study also reveals that intravenous iron supplementation exposed patients to a greater water supply due to iron dilution into saline solution. This trend is confirmed by the evaluation of the difference in the electrical resistance measured using a BIA analysis (**Table 2 and Figure 2**) [10].

Discussions

The therapy with Ferric Sodium EDTA, in combination with vitamin C, folic acid, copper gluconate, zinc gluconate and selenomethionine (Ferachel forte®) is a new iron formulation used for oral treatment of patients with secondary anaemia. Several studies showed the efficacy of Ferric Sodium EDTA in the treatment of IDA in different settings [7,11-20]. More data in literature underline that iron, along with Cu^{++}, Zn^{++}, Se^{++}, Vitamin C and Folic acid contribute to the normal function of the immune system. Iron is an essential element for the normal formation of red blood cells and hemoglobin that ensure normal oxygen transport to the entire body. Cu^{++} promotes the normal transport of iron into the body. Vitamin C increases iron absorption and its antioxidant activity can provide protective effects against eventual liver damage caused by iron overload. Folic acid co-operates with normal haematopoiesis [21-23]. We used this formulation in the first group of the study (**Table 1**) and we noted the real superiority in comparison with the intravenous administration of ferrous gluconate about arrhythmic risk, evaluated using T-peak-to-Tend index, and the risk of side effects due to high doses of saline solution administered intravenously in the second group of our study (**Table 2**). No concerns derived from eventual iron overload related to the high dose of Ferric Sodium EDTA combination (2 tabs/day) have been reported in this study, since liver parameters evaluated have been always in the normal ranges.

Table 2 Intravenous ferrous gluconate 63 mg/day into saline solution 500 mL, administered during the hospitalisation period (15 ± 5 days). The data are expressed as value ± DS.

	Control	Effect	P Value
Hb (g/dL)	8.9 ± 1.5	9.9 ± 1.9	**0.001**
Fe^{++} (mcg/dL)	19.6 ± 12.2	37.1 ± 21.9	**0.001**
RR (msec)	755.0 ± 243.4	779.0 ± 234.4	1.000
LF (msec)	1684.1 ± 2622.1	2016.5 ± 3191.1	0.818
HF (msec)	4601.1 ± 6561.2	3312.0 ± 4369.3	0.378
Tp-e (msec)	91.8 ± 16.2	99.1 ± 11.6	**0.048**
QTc (msec)	340.0 ± 42.8	352.7 ± 62.2	0.105
Tp-e/QTc	0.271 ± 0.04	0.282 ± 0.04	0.562
Resistance (Ω)	517.6 ± 139.6	503.6 ± 172.9	**0.018**
Reactance (Ω)	41.5 ± 19.5	38.5 ± 18.3	0.160

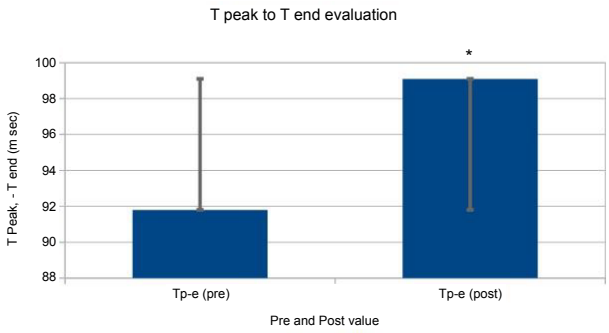

Figure 1 T-peak-to-T-end values in patients treated with intravenous ferrous gluconate 63 mg/day (into saline solution 500 mL).

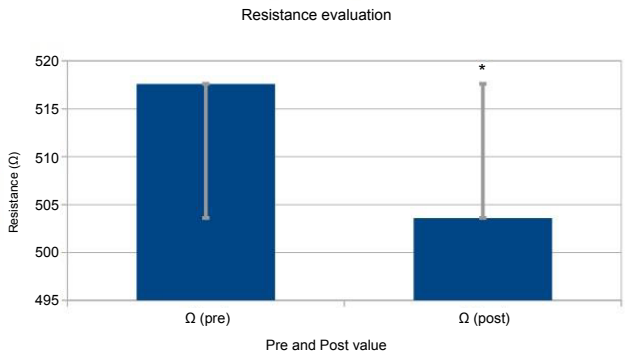

Figure 2 Resistance values in patients treated with intravenous ferrous gluconate 63 mg/day (into saline solution 500 mL).

Conclusion

The administration of Ferric Sodium EDTA, in combination with vitamin C, folic acid, copper gluconate, zinc gluconate and selenomethionine (Ferachel forte®) could be a valid alternative to ferrous gluconate, administered with intravenous therapy (gold standard) in the treatment of secondary anaemia in elderly patients. Our preliminary results are comfortable but not applicable to a broad spectrum of patients with secondary anaemia without a haematological evaluation of the different causes of anaemia.

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