



Effect of Ferric Sodium EDTA administration, in combination with vitamin C, folic acid, copper gluconate, zinc gluconate and selenomethionine, on cardiovascular risk evaluation: exploration of the HRV frequency domain

Abstract

Background: Anaemia is a frequent co-morbidity in old patients affected by chronic heart failure and/or respiratory diseases. Using the Heart Rate Variability (HRV) analysis is possible to provide an evaluation of the safety and the effectiveness of intervention.

Objective: To evaluate 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, by exploring the HRV frequency domain.

Methods: In 45 elderly patients with secondary anaemia and/or low-moderate kidney failure, laboratory values after administration of Ferric Sodium EDTA, 2 tabs a day, in combination with vitamin C, folic acid, copper gluconate, zinc gluconate and selenomethionine (Ferachel forte®) for 24 days (N=16 patients) or ferrous gluconate 63 mg/day added to saline solution, administered using intravenous access during the hospitalization period of 15 ± 5 days (N=29 patients) were evaluated. Also, ECG signals and bioelectrical impedance (BIA) were measured.

Results: Oral iron supplementation with Ferric Sodium EDTA, in combination with vitamin C, folic acid, copper gluconate, zinc gluconate and selenomethionine (Ferachel forte®) confirmed to be effective and safe about the cardiovascular risk in old patients. This study showed the real superiority of the oral administration about the cardiovascular risk in elderly patients in comparison with intravenous administration of ferrous gluconate.

Conclusion: This study confirms that Ferric Sodium EDTA combination (Ferachel forte®) can be a valid alternative to ferrous gluconate intravenous therapy (gold standard) in the treatment of secondary anaemia in elderly patients. In fact, during the treatment, efficacy results have been maintained without statistically significant variations about cardiovascular risk, evaluated by exploring the HRV frequency domain.

Keywords: Anaemia, cardiovascular risk, ferric sodium EDTA, spectral analysis, HRV frequency domain, elderly, kidney failure

Introduction

All causes of anaemia give a reduction of haemoglobin level and red blood cells value and haematological problems have a high impact on the quality of life. Anaemia is defined as a condition in which the body has a decreased number of circulating erythrocytes, or Red Blood Cells (RBCs), that become insufficient to meet the body's physiologic needs.

Consequently, anaemia can also be defined as a decreased hemoglobin concentration or RBC mass compared with age-matched controls. The World Health Organization (WHO) defines anaemia as a Haemoglobin (Hb) less than 13 g/dL in adult men and less than 12 g/dL in non-pregnant adult women [1].

Iron deficiency (ID) and Iron-Deficiency Anaemia (IDA) are globally recognized, in daily

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clinical practice, as frequent medical conditions. ID is defined as a level's reduction of total body iron, especially iron stores, with preservation of levels of erythroid iron. IDA is a more severe condition in which low levels of iron are associated with anaemia and the presence of microcytic hypochromic red cells [2].

Anaemia is a common, multi-factorial, relatively mild condition in elderly, with Hb levels near 10-11g/dL in most subjects. However, it can be associated with a variety of adverse outcomes, including longer hospitalization, disability, and increased mortality risk [3].

Regarding Hb threshold to be used to define anaemia in elderly individuals, discussions have been reported, since WHO criteria were based on statistical distributions in reference samples that did not include individuals >65 years of age. Several studies reported that a Hb value <12 g/dL is commonly considered indicative of anaemia in elderly of both sexes, since Hb values in apparently healthy elderly individuals are generally lower than those in younger adults and the differences between males and females tend to disappear with aging [3,4].

In old patients, the main causes of anaemia are Iron Deficiency Anaemia (IDA) and anaemia of chronic diseases (or functional ID), that can be affected by several factors, including malnutrition, delay gastric emptying and occult blood loss [5].

In elderly, Chronic Gastrointestinal (GI) diseases represent the most frequent causes of ID and IDA, leading to both iron loss and malabsorption. Chronic upper and lower GI blood losses can be related to a variety of pathologies like esophagitis, gastritis, peptic ulcer, Inflammatory Bowel Disease (IBD), neoplastic disease, and ano-rectal lesions, such as haemorrhoids. Furtherly, GI bleeding is increased in multimorbidity patients, taking concomitantly chronic medications, like Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and/or antithrombotic therapies [3,5].

Malnutrition can be associated with inadequate dietary iron intake and absorption and can be worsen by decline of biological and cognitive functions, i.e. a reduction of appetite and of taste sensation. Also, depressive syndromes, particularly frequent in older populations, are recognized to be associated with

a worsening of nutritional state. Furthermore, in depressive disorders occurs dysregulation of the neuroendocrine and sympathetic nervous systems, potentially affecting erythropoiesis [3,5,6].

Iron malabsorption is also relatively frequent in the elderly and can be affected by *Helicobacter pylori* (HP) infection, autoimmune atrophic gastritis, celiac disease, IBD, and long-term use of Proton Pump Inhibitors (PPI) [3,5].

Several studies evaluated anaemia frequency in older adults, showing a range from 8% to 25%, with increased percentage in subjects older than 85 years old. In this population, anaemia can influence mortality and cognitive/physical performance, increasing number of falls and hospitalizations. Therefore, the evaluation of iron blood level and the relative treatment or follow-up is crucial [3,5].

Recent studies underline that iron administration is associated with improvements of cardiovascular outcomes and quality of life [2,7,8].

Using the Heart Rate Variability (HRV) analysis of the spectral components in the frequency domain is possible to explore the neurovegetative system. Numerous physiological conditions and diseases have an impact factor on the dimension of the area of each peak of frequency range on the HRV power spectrum. Some studies have used spectral HRV and blood pressure variability analysis in a large group of patients and it has been observed that the increase in total HRV and LF power is associated with survival, while the progressive decreases of HRV have been associated with deterioration and death. Alterations of the spectral analysis are correlated with the severity of the disease, the use of this method for the assessment of the state of cardiac and non-cardiac diseases, could provide an evaluation of the prognosis and determine the effectiveness of intervention [9,10].

■ Aim of the study

The aim of this study is to confirm 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 a day for a treatment period of 24 days, in elderly patients with secondary anaemia, about cardiovascular risk and quality of life, explored by HRV frequency domain evaluation.

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Methods

45 elderly patients (age $79,4 \pm 10,1$ years old) with a recent diagnosis of secondary anaemia due to iron deficiency and/or low-moderate kidney failure were enrolled. The patients were divided into 2 groups: 16 patients were treated with oral administration of Ferric Sodium EDTA 2 tabs a day, corresponding to 60 mg of iron, in combination with vitamin C, folic acid, copper gluconate, zinc gluconate and selenomethionine (Ferachel forte®) for 24 days; 29 patients were treated with ferrous gluconate 63 mg/day added to saline solution administered using intravenous access during the hospitalization period of 15 ± 5 days. The enrolled patients had low-moderate kidney failure (mean creatinine value: $1,1 \pm 0,6$ mg/dL in the group with oral administration of Ferric Sodium EDTA combination and $1,4 \pm 1$ mg/dL in the group with intravenous administration of ferrous gluconate). Improvement of laboratory values, such as haemoglobin and sideraemia level, and electrocardiographic trace with a length of 2-5 minutes before and after the administration of Ferric Sodium EDTA combination or ferrous gluconate, were evaluated.

Also, the ECG signal and the Bioelectrical Impedance (BIA) were measured. For the ECG signal analysis, Cardio CE palm version 2.0 (XAI-Medica) was used to register standard ECG and beat to beat ECG for Heart Rate variability evaluation. The Bioelectrical Impedance Analysis (BIA) has been analyzed with the Bodygram PRO 3,0 (Akern).

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 [11].

Using a short registration of the electrocardiograph with a length of 2-5 min, the spectral analysis reveals three main peaks, describable as the VLF (very low frequency) that includes very low frequencies with values between 0 and 0.04 Hz that are influenced by the regulation of the temperature and from the humoral systems, the LF (low frequency) that includes low frequencies between 0.04-0.15 Hz, that are associated both to the sympathetic modulation and to the sympatho-vagal modulation depending on the baroreceptive control index of activation of the sympathetic system, the HF (high frequency) which includes

the frequencies between 0.15-0.4 Hz, that are associated with parasympathetic activation index, and reflect the vagal modulation of the sinus rhythm associated with the respiratory arrhythmia and finally the Total Power which is the sum of the three peaks or the sum of the single spectral powers (VLF+LF+HF) [9,10].

Statistical analysis is performed using Paired T-test with Sigmatat v. 3.5 analysis program. Differences were considered significant when $P < 0,05$.

Results

Data collected in this study confirm that oral treatment with Ferric Sodium EDTA, in combination with vitamin C, folic acid, copper gluconate, zinc gluconate and selenomethionine (Ferachel forte®) at the dosage of 60 mg (2 tabs a day) is an efficacy and safety treatment as preliminary referred. Both results in hemoglobin (Hb) and sideraemia levels showed that treatment with oral iron supplementation for 24 days is as effective as intravenous iron infusion, administered 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 (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 group.

■ Safety results

Treatment with Ferric Sodium EDTA in combination with vitamin C, folic acid, copper gluconate, zinc gluconate and selenomethionine (Ferachel forte®) did not modify ECG parameters, without bringing concerns about high liquid amounts administered to such a sensitive patient population, such is the elderly patient with low-moderate kidney failure (TABLE 1).

Data showed that intravenous iron supplementation exposes patients to a greater water supply due to iron dilution into saline solution. Intravenous iron supplementation gave a statistically significant variation of the T-peak to T-end value that represents a predictive

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 \pm Standard Deviation (DS).

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

TABLE 2. Intravenous ferrous gluconate 63 mg/day into saline solution 500 mL, administered during the hospitalisation period (15 \pm 5 days).

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

parameter of arrhythmic risk (**FIGURE 1**). This trend is confirmed by the evaluation of the difference in the electrical resistance measured using a bioimpedenziometric test (**FIGURE 2**).

More interesting data are noted analyzing electrocardiographic results regarding HRV frequency domain after the treatment with Ferric Sodium EDTA combination at the dosage of 60 mg/day for 24 days (**TABLE 3** and **FIGURE 3**), because this positive trend is confirmed by the absence of statistically significant reduction ($p=0.097$) of the vagal tone using the Fast Fourier Transformation analysis or FFT-HF (**TABLE 3**) and the relative statistically significant reduction ($p=0.049$) of the vagal tone using the Auto-regressive Analysis or AR-HF (**TABLE 3** and **FIGURE 3**). In the patients enrolled in this study, the oral administration confirms the safety of the treatment at high dosage (2 tabs a day).

Discussion

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. Ferric Sodium EDTA is a novel iron source that already reported large efficacy and safety data in several setting, such as anaemic pregnant women [12-14], anaemic pre-school and school-aged children and adolescents [15-19].

In addition, several meta-analyses concluded that Ferric Sodium EDTA, already as single component, is highly effective in controlling iron deficiency and reducing the prevalence of iron-deficiency anaemia in men, women, and children [20-22]. Furtherly, Ferric Sodium EDTA is recommended for the mass fortification of high-phytate cereal flours and for sauces with a high peptide content (e.g. fish sauce, soy sauce), by the WHO Guidelines on food fortification with micronutrients.

The use of Ferric Sodium EDTA in combination with vitamin C, folic acid, copper gluconate, zinc gluconate and selenomethionine (Ferachel forte®) was evaluated in elderly patients with secondary anaemia due to iron deficiency and/or low-moderate kidney failure, since this population is often exposed to adverse events related to intravenous iron therapy. These events can be related to injection site, such as phlebitis

Tpeak to T end index

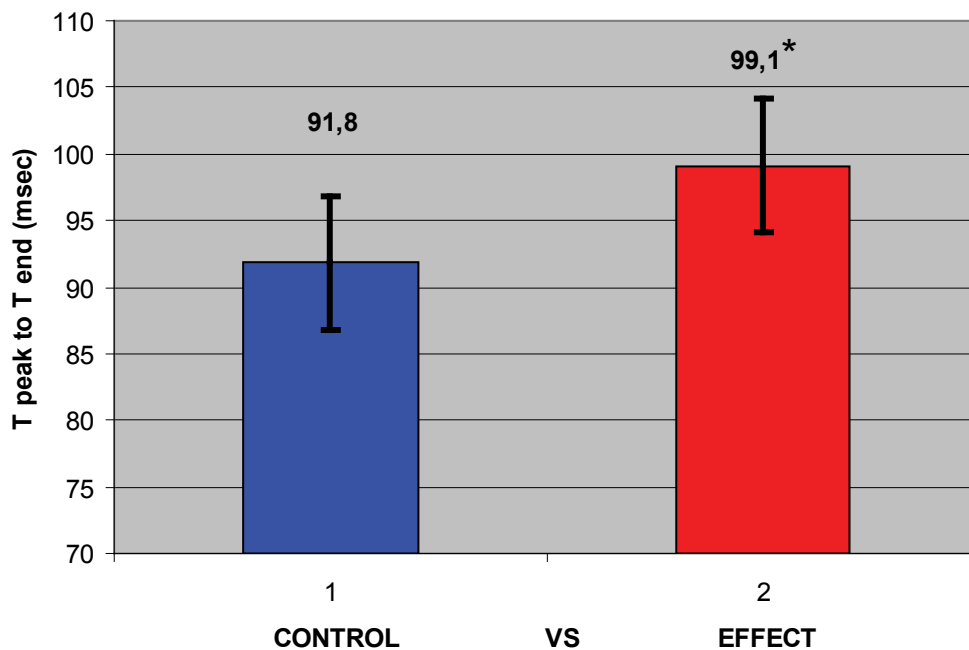


FIGURE 1. Descriptive Analysis of the Tpeak to Tend index in the group treated with intravenous ferrous gluconate therapy 63 mg/day (in saline solution 500 mL).

RESISTANCE

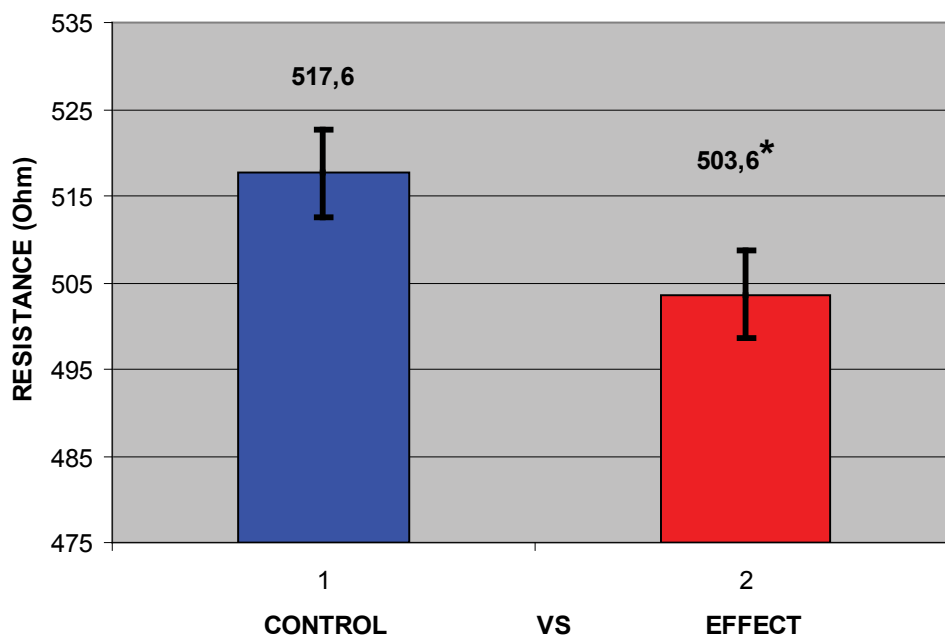


FIGURE 2. Descriptive Analysis of the Bioelectrical Impedance Analysis (BIA) in the group treated with intravenous ferrous gluconate therapy 63 mg/day (in saline solution 500 mL).

and thrombophlebitis, and/or can increase the risk of allergic reactions and/or aggravate pre-existing conditions such as heart failure or renal failure.

The results showed treatment efficacy (TABLE 1) and safety (TABLE 3) of the oral

iron formulation. In particular, data pointed out the real superiority of the oral administration about the cardiovascular risk analysed exploring the HRV frequency domain in old patients in comparison with the intravenous administration of ferrous gluconate (FIGURE 3).

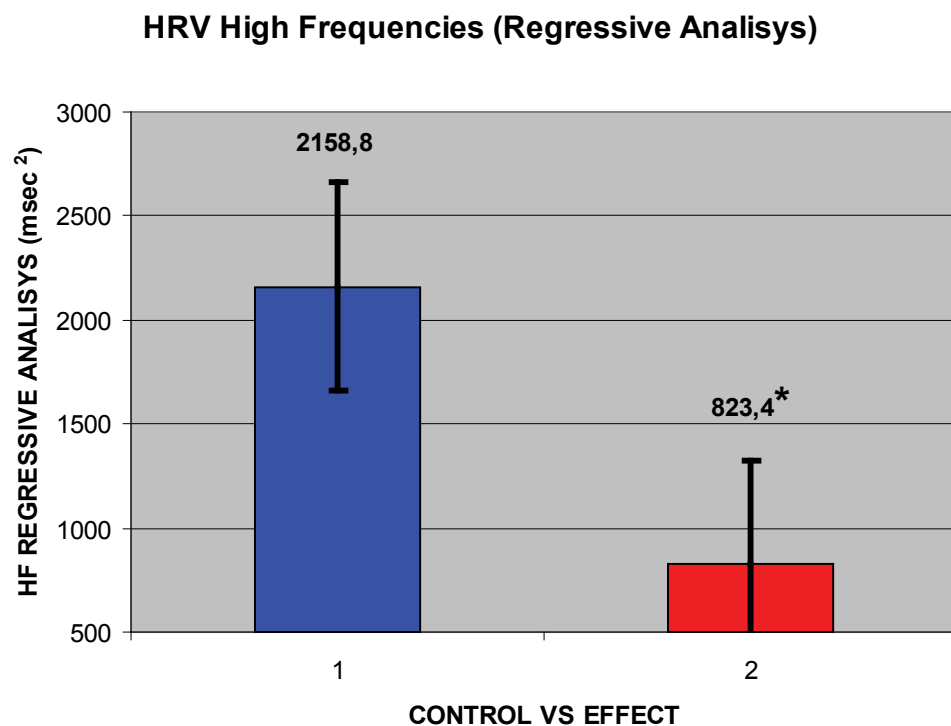


FIGURE 3. Descriptive Analysis of the HRV High Frequencies ($p=0.049$) explored by Regressive Analysis in the group treated with Ferric Sodium EDTA in combination with vitamin C, folic acid, copper gluconate, zinc gluconate and selenomethionine (Ferachel forte®) 2 tabs/day for 24 days.

TABLE 3. Ferric Sodium EDTA in combination with vitamin C, folic acid, copper gluconate, zinc gluconate and selenomethionine (Ferachel forte®) 2 tabs/day for 24 days.

	Control	Effect	$p<0.050$
fft-LF	2254.5 ± 3471.6	858.0 ± 1140.1	0.145
fft-HF	2704.8 ± 3982.5	883.8 ± 964.9	0.097
fft-TOTAL	8447.1 ± 1746.9	2290.4 ± 2404.5	0.188
fft-LF/HF	0.813 ± 0.589	1.062 ± 0.930	0.335
AR-LF	1817.8 ± 2629.3	1024.3 ± 1419.1	0.313
AR-HF	2158.8 ± 2622.4	823.4 ± 810.6	0.049*
AR-TOTAL	6398.6 ± 1012.8	1012.8 ± 3345.5	0.193
AR-LF/HF	0.811 ± 0.659	0.858 ± 0.762	0.806

These preliminary results are comfortable but not applicable to a broad spectrum of patients with secondary anaemia.

Conclusion

This study confirms that Ferric Sodium EDTA in combination with vitamin C, folic acid, copper gluconate, zinc gluconate and selenomethionine (Ferachel forte®) is a valid and safe alternative to ferrous gluconate intravenous therapy (gold standard) in the treatment of secondary anaemia in elderly patients, because during the treatment efficacy results has been maintained without statistically significant variations about cardiovascular risk, evaluated exploring the HRV frequency domain.

Conflict of Interest

The authors declare that they have no conflict of interest.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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