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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

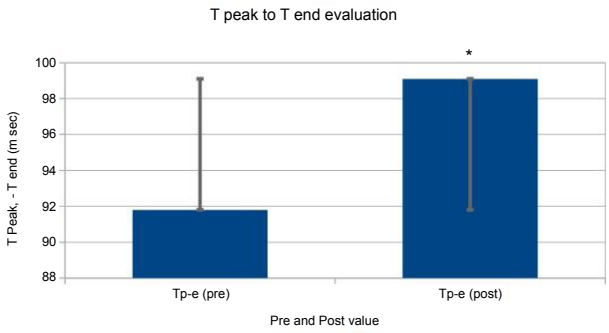

Figure 1 T-peak-to-T-end values in patients treated with intravenous ferrous gluconate 63 mg/day (into saline solution 500 mL).

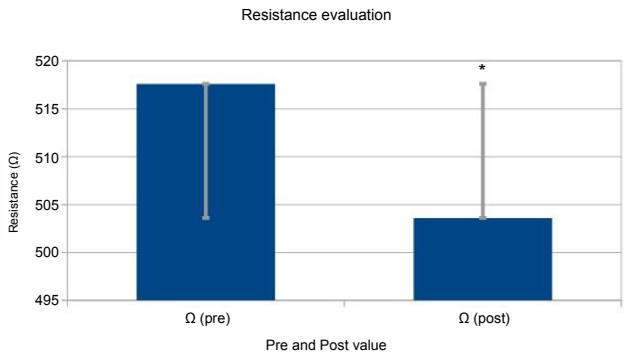

Figure 2 Resistance values in patients treated with intravenous ferrous gluconate 63 mg/day (into saline solution 500 mL).

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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Ruolo del ferro sodico EDTA associato a vitamina C, acido folico, gluconato di rame, gluconato di zinco e selenometionina in pazienti con anemia secondaria: effetti sul valore dell'emoglobina e sul rischio cardiovascolare.

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Abstract

INTRODUZIONE: L'anemia sideropenica (IDA) ha un forte impatto sulla qualità della vita nei pazienti anziani affetti da insufficienza cardiaca cronica e/o malattie respiratorie. Lo scopo di questo studio è di valutare l'efficacia e la sicurezza del ferro sodico EDTA in combinazione con vitamina C, acido folico, gluconato di rame, gluconato di zinco e selenometionina (Ferachel forte®) 2 compresse/die per 24 giorni, nei pazienti anziani con anemia secondaria, analizzando il rischio cardiovascolare e la qualità della vita, mediante analisi ECG e di bioimpedenziometria (BIA).

MATERIALI E METODI: Abbiamo arruolato nello studio 43 pazienti anziani, divisi in 2 gruppi: il primo gruppo (N = 14 pazienti) è stato trattato con la somministrazione orale di ferro sodico EDTA in combinazione con vitamina C, acido folico, gluconato di rame, gluconato di zinco e selenometionina (Ferachel forte®) 2 compresse/die, contenenti 60 mg di Fe^{3+}, per 24 giorni, il secondo gruppo (N = 29 pazienti) è stato trattato con gluconato ferrico 63 mg/die disciolto in una soluzione salina somministrata mediante accesso endovenoso durante il periodo di ricovero ospedaliero di 15 ± 5 giorni. Abbiamo valutato i valori dei globuli rossi, dell'emoglobina (Hb) e il profilo ematico dei pazienti. Abbiamo anche misurato i parametri dell'ECG e di bioimpedenziometria (BIA).

RISULTATI: Questo studio ha dimostrato che il trattamento orale con la combinazione di ferro sodico EDTA al dosaggio di 60 mg (2 compresse/die) è efficace per il miglioramento dei livelli ematici di Hb e sideremia. La somministrazione endovenosa di ferro espone i pazienti a un maggiore apporto idrico, confermato dall'analisi BIA, e fornisce una variazione statisticamente significativa dell'indice T-peak- to-T-end, parametro predittivo del rischio aritmico.

CONCLUSIONI: La terapia con ferro sodico EDTA, in combinazione con vitamina C, acido folico, gluconato di rame, gluconato di zinco e selenometionina (Ferachel forte®) ha mostrato una reale superiorità e potrebbe essere una valida alternativa alla terapia endovenosa con ferro gluconato nel trattamento dell'anemia secondaria nei pazienti anziani.

Keywords: Anemia sideropenica, rischio cardiovascolare, insufficienza renale, Ferro Sodico EDTA, anziano, qualità della vita.

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INTRODUZIONE

La carenza di ferro (ID) è un problema globale che colpisce oltre due miliardi di persone in tutto il mondo. I pazienti con ID mostrano livelli ridotti di ferro totale, in particolare livelli ridotti dei depositi di ferro, ma restano invariati i livelli di ferro eritroideo.

[illegible]

MATERIALI E METODI

[illegible]

SOGGETTI STUDIATI

I pazienti reclutati (età: 78,2 ± 13,1 anni) hanno ricevuto una diagnosi di anemia secondaria dovuta a carenza di ferro e ad insufficienza renale moderata (valore medio della creatinina: 1,1 ± 0,6 mg/dL nel gruppo trattato con la somministrazione orale di ferro sodico EDTA e 1,4 ± 1 mg/dL nel gruppo trattato con la somministrazione endovenosa). Abbiamo valutato i valori ematici dei globuli rossi, Hb e sideremia. Abbiamo stimato il miglioramento dei valori di laboratorio e l'aderenza alla terapia prima e dopo la somministrazione della combinazione di ferro sodico EDTA rispetto alla terapia con gluconato ferrico.

Per l'analisi dei segnali ECG, abbiamo utilizzato Cardio CE palm versione 2.0 (XAI-Medic) per registrare l'ECG standard e battito per battito per la valutazione della variabilità della frequenza cardiaca (HRV). Utilizzando una breve registrazione della traccia elettrocardiografica sono stati misurati l'indice T peak to T end (Tp / Te) e l'intervallo Qt corretto (QTc). [8]

L'impedenza bioelettrica (BIA) è stata analizzata con Bodygram PRO 3,0 (Akern). [9] Abbiamo usato la scala internazionale per i test di laboratorio (creatinina mg/dL). L'analisi statistica è stata eseguita utilizzando il test dei segni per ranghi di Wilcoxon (Z) con il programma di analisi Sigmastat v. 3.5.

RISULTATI

Questo studio ha dimostrato che il trattamento orale con ferro sodico EDTA, in combinazione con vitamina C, acido folico, gluconato di rame, gluconato di zinco e selenometionina (Ferachel forte®) alla dose di ferro di 60 mg (2 compresse/die) è efficace per il miglioramento dei livelli sierici di Hb e di ferro. I risultati hanno mostrato livelli aumentati sia di Hb che di sideremia, con un andamento simile tra la somministrazione orale di ferro per 24 giorni e l'infusione di ferro per via endovenosa, somministrata durante il periodo di ricovero (15±5 giorni). In particolare, i livelli di Hb sono aumentati da 9,5±1,3 g/dL a 11,7±1,9 g/dL (P=0,001) nel gruppo trattato con la combinazione di ferro sodico EDTA (Tabella 1). Il corrispondente aumento dei livelli di Hb nel gruppo trattato con ferro per via endovenosa era compreso tra 8,9±1,5 g/dL e 9,9±1,9 g/dL (P = 0,001; Tabella 2). Sono stati ottenuti risultati simili per i livelli di sideremia: da 19,5±5,6 mcg/dL a 53,8±25,9 mcg/dL (P = 0,001; Tabella 1) per il gruppo sottoposto a somministrazione orale di ferro; e da 19,6±12,2 mcg/dL a 37,1±21,9 mcg/dL (P = 0,001; Tabella 2) per il gruppo trattato con terapia endovenosa.

Table 1 [illegible]

	Controllo	Effetto	P Value
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
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[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]

Inoltre, i nostri dati hanno mostrato che il trattamento orale con la combinazione di ferro sodico EDTA è ben tollerato (Tabella 1). Durante lo studio, non sono stati segnalati eventi avversi correlati al sovraccarico di ferro, né al livello di ferro nel fegato né come emolisi. Solo un paziente ha manifestato diarrea transitoria che è stata risolta riducendo la dose di ferro sodico EDTA a 30 mg di Fe^{3+} (1 compressa/die). L'analisi dell'HRV non ha mostrato alcuna differenza statistica nei valori, ma analizzando i segnali elettrocardiografici i nostri dati hanno mostrato una variazione statisticamente significativa dell'indice T-peak-to-T-end in pazienti con supplementazione endovenosa di ferro (Tabella 2 e Figura 1). In questi pazienti, l'indice T-peak-to-T-end era statisticamente più elevato rispetto ai pazienti in trattamento con terapia orale di ferro. Questo dato rappresenta un parametro predittivo del rischio aritmico. Il nostro studio rivela anche che l'integrazione di ferro per via endovenosa ha esposto i pazienti a un maggiore apporto idrico a causa della diluizione del ferro in soluzione salina. Questo risultato è confermato dalla valutazione della differenza nella resistenza elettrica misurata mediante l'analisi BIA (Tabella 2 e Figura 2). [10]

DISCUSSIONI

La terapia con ferro sodico EDTA, in combinazione con vitamina C, acido folico, gluconato di rame, gluconato di zinco e selenometionina (Ferachel forte®) è una nuova formulazione di ferro utilizzata per il trattamento orale di pazienti con anemia secondaria. Diversi studi hanno dimostrato l'efficacia del ferro sodico EDTA nel trattamento dell'IDA in contesti differenti. [7,11-20]

Tabella 2 Ferro gluconato 63 mg/die disciolto in una soluzione salina di 500 mL, somministrata durante il period di ricovero (15 ± 5 giorni). I dati sono riportati come Deviazione Standard + DS.

	Controllo	etto	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
Resistenza (Ω)	517.6 ± 139.6	503.6 ± 172.9	**0.018**
Reattanza (Ω)	41.5 ± 19.5	38.5 ± 18.3	0.160

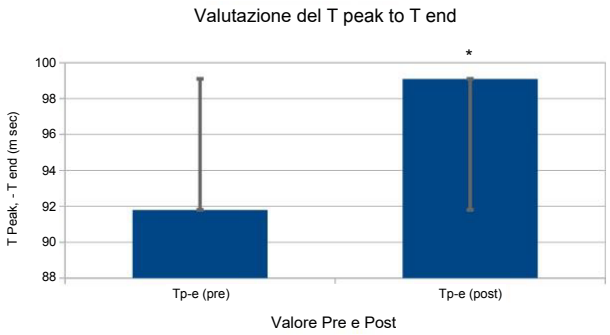

Figura 1 Valori del T-peak-to-T-end in pazienti trattati con gluconato ferrico intravenoso 63 mg/die (disciolto in una soluzione salina da 500 mL).

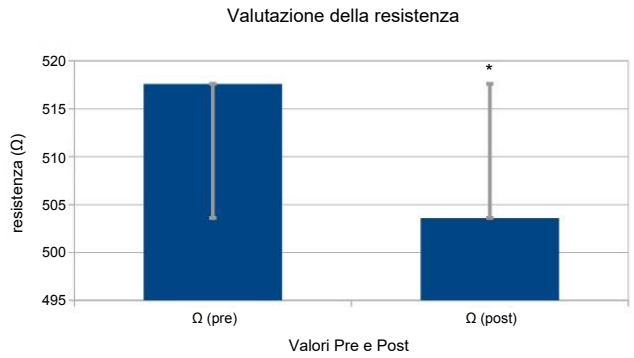

Figura 2 Valori della Resistenza in pazienti trattati con gluconato ferrico intravenoso 63 mg/die (disciolto in una soluzione salina di 500 mL).

Ulteriori dati in letteratura sottolineano che ferro, insieme a Cu^{++}, Zn^{++}, Se^{++}, Vitamina C e acido folico contribuiscono alla normale funzione del sistema immunitario. Il ferro è un elemento essenziale per la normale formazione dei globuli rossi e dell'emoglobina che assicurano il normale trasporto di ossigeno in tutto il corpo. Cu^{++} promuove il normale trasporto di ferro nel corpo. La vitamina C aumenta l'assorbimento del ferro e la sua attività antiossidante può fornire effetti protettivi contro eventuali danni al fegato causati da sovraccarico di ferro. L'acido folico coopera con l'ematopoiesi normale [21-23]. Abbiamo usato questa formulazione nel primo gruppo di studio (Tabella 1) e abbiamo notato la reale superiorità rispetto alla somministrazione endovenosa di gluconato ferrico in merito al rischio aritmico, valutata utilizzando l'indice T-peak-to-T-end e il rischio di effetti dovuti ad alte dosi di soluzione salina somministrata per via endovenosa nel secondo gruppo del nostro studio (Tabella 2). Inoltre, non sono state riportate segnalazioni derivanti da un eventuale sovraccarico di ferro correlato alla dose elevata di combinazione di ferro sodico EDTA (2 compresse/die), poiché i parametri epatici valutati sono sempre stati nella norma.

CONCLUSIONI

La somministrazione del ferro sodico EDTA, in combinazione con vitamina C, acido folico, gluconato di rame, gluconato di zinco e selenometionina (Ferachel forte®) potrebbe essere una valida alternativa al gluconato ferrico, somministrato con terapia endovenosa (gold standard) nel trattamento dell'anemia secondaria nei pazienti anziani. I nostri risultati preliminari sono sufficienti ma non applicabili ad un ampio spettro di pazienti con anemia secondaria senza una valutazione ematologica delle diverse cause di anemia.

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