ORIGINAL ARTICLE

Angina pectoris and intensive intravenous iron treatment in hemodialysis patients

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Abstract

Background: Intravenous iron and erythropoietin are commonly used for the treatment of anemia in end stage renal disease (ESRD) patients. Even though i.v. iron is proven to be very effective, there is great concern regarding its possible toxic effects. The aim of our study was to evaluate the possible correlation between iron administration and the incidence of angina pectoris in hemodialysis patients. Methods: The study sample consisted of 10 stable coronary heart disease patients, receiving chronic hemodialysis treatment. The patients followed consecutively three different i.v. iron dose regimens according to their needs. Their standard monthly laboratory measurements were correlated with the incidence of angina pectoris and i.v. iron treatment. Results: Hematocrit, ferritin, serum iron and mean rhEPO dose were related to the total amount of administered iron. Angina pectoris was related to intensive iron treatment, age and platelet count. Total white blood cell count were related to hemodialysis duration, platelet count and serum triglycerides. Conclusion: It is suggested that the intensive intravenous iron treatment (300mg/week) is associated with the increased incidence of angina pectoris in stable coronary heart disease patients receiving hemodialysis. *Hippokratia 2007; 11, (1):30-34*

Key words: *coronary heart disease, angina pectoris, intravenous iron, erythropoietin, ESRD*

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Cardiovascular disease (CVD) represents the leading cause of death in end stage renal disease (ESRD) patients[1]. It is estimated that more than 50% of deaths are due to CVD in ESRD patients.[2] Cardiovascular mortality in these patients is estimated to be 10 to 20 times higher than in the general population, even after correction for demographic and comorbidity characteristics.[3] Traditional risk factors for CVD are present since the early stages of chronic kidney disease[4]. Apart from the traditional factors, hemodynamic overload, anemia, electrolyte disorders and oxidative stress are almost invariably present in ESRD patients[4-6].

Since the very beginning of renal replacement therapy anemia represented a common problem in hemodialysis patients. According to the NKF-K/DOQI clinical practice guidelines for anemia of chronic kidney disease, the target range for hemoglobin/hematocrit (Hb/Ht) should be between 11g/dl (33%) and 12g/dl (36%)[7]. These indications are in accordance with annual cohorts of hemodialysis (HD) patients that have shown that patients with an Ht level between 33% – 36% had an 8% lower death rate than those with values between 30% – 33%[8]. As part of common practice erythropoietin (rhEPO) is administered, since it has been proven to be highly effective in the treatment of anemia in ESRD patients. Not all patients respond to this treatment. The commonest cause of hyporesponsiveness to rhEPO therapy is inadequate supply of sufficient iron needed for erythropoiesis[9]. In order for patients to achieve and maintain these Ht levels, sufficient iron should be administered to maintain a transferrin saturation percent of ≥ 20% and a serum ferritin level of ≥ 100ng/ml[7]. Additionally, study results of published original research concluded that the chronic administration of intravenous iron can reduce recombinant human erythropoietin requirements, effect achieved by maximizing iron stores[10,11]. It has been shown that even in the iron-replete patients, i.v. iron supplementation enhanced hemoglobin response to rhEPO with an additional lowering of dosage requirements of rhEPO[11-13]. The estimated need of iron is 1.5 – 2 gr per year[14]. The most widely used i.v. iron preparations for HD patients are: iron dextran, iron sucrose, iron gluconate and iron dextrin (polymaltose)[15,16]. Even though i.v. iron is proven to be very effective in the treatment of anemia, there is great concern regarding the possible toxicity of iron administration[17].

Methods

Study design

The aim of our study was to evaluate the possible correlation between the parenteral iron administration and the incidence of angina pectoris in the ESRD patients.

Patient selection

The study sample consisted of 10 patients who were

receiving hemodialysis treatment three times a week, for a duration of four hours each time, for at least 18 months and whose angina was reasonably stable. Patients with acute liver disease, acute or chronic infectious disease, severe anemia (Ht<32%), or unable to follow their usual medication were also excluded. Their medical files have been reviewed thoroughly. Patient characteristics are shown in Table 1.

Table 1: *Patient characteristics*

	Mean	Std Deviation
Age (years)	64.4	±12.12
Sex (M/F)	6/4	
BMI	25.4 kg/m^2	±3.9
Diabetes mellitus	5	
Hypertension	7	
Dialysis frequency	3 sessions/week	0
Dialysis duration	40.6 months	±19.4
SBP	144.0mmHg	±16.6
DBP	72.0mmHg	±10.1
Heart rate	74/min	±8

NOTE: BMI= Body Mass Index; SBP= Systolic Blood Pressure; DBP= Diastolic Blood Pressure.

Information regarding the i.v. iron treatment and rhEPO were obtained from the patients medical files. Recombinant erythropoietin (rhEPO) was prescribed in order to maintain predialysis Ht at 33 to 36%. Iron was used in the form of iron sucrose dissolved in 100ml normal saline and administered during the last half hour of dialysis, aiming at a serum ferritin level between 600-800ng/ml.

Laboratory data were based on predialysis "monthly measurements" and were those of the preceding month from each episode of angina. This decision was based mainly on the fact that serum ferritin represents also an acute phase marker and measurements that were made at the time or near after an acute coronary event might be misleading. These measurements included hematocrit, total white blood cell count (WBC), platelets count (PLT), serum creatinine, urea, uric acid, ESR, iron, ferritin, sodium, potassium, calcium, phosphorus, phosphate alkaline, glucose, total cholesterol, triglycerides, total proteins and albumin. All values are expressed as mean ± sd. Table 2.

The total number of weeks for which the patients received 100 mg, 200 mg, or 300 mg of iron sucrose were calculated, as well as the total iron dose and the mean iron dose administered. The administration of 300mg of iron per week was considered as the "intensive" iron treatment. The dose regimen during the incidents was also taken into consideration. The mean rhEPO per week and the total rhEPO dose received by each patient were also calculated.

Statistical analysis

Standard descriptive statistics were used for all patient characteristics, laboratory values, iron dose and rhEPO dose. In order to examine the possible association of i.v. iron and rhEPO administration with demographic and laboratory values, multivariable analyses were conducted. Pearson's Correlation Coefficient was used to determine the correlations among the parameters, while Spearman's rho was used for skewed data when appropriate. For statistical analysis purposes, patients were divided in three different treatment-related periods: period 1 represented the time during which the patients received 100 mg of i.v. iron per week, period 2 represented the time during which the patients received 100mg of i.v. iron twice weekly (200 mg/week) and period 3 represented the time during which the patients received 100mg of i.v. iron thrice weekly (300 mg/week). One Way Analysis of Variance was used to assess whether the incidence of angina pectoris differed between groups. All p-values are two sided and were considered statistically important when $p<0.05$. Confidence intervals represent 95% intervals.

Table 2: *Laboratory data*

	Mean	Std Dev.	Min	Max
Hematocrit (%)	36.2%	3.1	32	42
WBC (x10^3/μl)	7.3	2.5	4.5	13.1
PLT (x10^3/μl)	201.5	54.6	136.0	300.0
ESR (1st hour)	55.6	28.1	24	115
Urea (mg/dl)	128.6	28.1	95	179
Creatinine (mg/dl)	8.4	2.3	5.7	13.8
Uric acid (mg/dl)	7.2	1.5	4.7	9.1
Glucose (mg/dl)	137	83	75	373
Sodium (mEq/L)	143.1	4.5	138	152
Potassium (mEq/L)	5.0	0.9	3.9	7.0
Calcium (mg/dl)	9.3	1.2	7.9	12.5
Phosphorus (mg/dl)	4.8	1.3	3.0	7.6
CaxP product	45.6	15.7	25.2	83.7
Phosphatase alkaline (U/L)	104.2	69.5	50	313
Total cholesterol (mg/dl)	173.4	35.2	133	241
Triglycerides (mg/dl)	177	80.0	80	341
HDL-cholesterol (mg/dl)	39.8	12.3	27	55
Total protein (g/dl)	6.9	0.6	5.9	7.9
Albumin (g/dl)	3.8	0.5	3.0	4.9
Serum Iron (μg/ml)	75.5	55.2	32	227
Serum Ferritin (ng/ml)	711.7	610.6	30	2006

NOTE: To convert urea in mg/dl to mmol/L, multiply by 0.17; serum creatinine in mg/dl to μmol/L, multiply by 88.4; uric acid in mg/dl to mmol/L, multiply by 0.05948; glucose in mg/dl to mmol/L multiply by 0.555; Phosphorus in mg/dl to mmol/L, multiply by 0.3229; Total cholesterol in mg/dl to mmol/L, multiply by 0.0259; Triglycerides in mg/dl to mmol/L, multiply by 0.01129; HDL-cholesterol in mg/dl to mmol/L, multiply by 0.0259; Serum iron in μg/dl to μmol/L, multiply by 0,1791.

Table 3: *Correlated parameters*

Correlated parameters	correlation coefficient (CC)	p (significance)
Hematocrit / serum iron	0.711	p<0.001
Hematocrit / total iron	0.639	p<0.038
Serum iron / total iron	0.872	p<0.001
Ferritin / total iron	0.673	p<0.023
Ferritin / mean rhEPO dose	-0.681	p<0.015
Total iron / mean rhEPO dose	-0.597	p<0.052
WBC / HD duration	0.820	p<0.001
WBC / serum triglycerides	0.566	p<0.055
Tot. cholesterol / serum triglycerides	0.580	p<0.048
WBC / platelet count	0.629	p<0.028
300mg iron / platelet count	0.563	p<0.057
Angina incidence / platelet count	0.591	p<0.043
Angina incidence / age	0.605	p<0.037
Angina incidence / 300mg iron	0.665	p<0.018

NOTE: all p-values are two sided

Results

Ten patients met the criteria accepted for the study. They were receiving hemodialysis treatment three times a week, for a duration of four hours each time, for a mean period of 40.6 ± 19.4 months (min: 22; max: 84). Their angina was reasonably stable and accurate data referring their treatment could be assessed from their medical files. Six patients were men and four women. Their mean age was 64.4 ±12.1 years (min: 43; max: 79). Half of them were diabetic and seven were hypertensive. Their mean BMI was 25.4 ±3.9. The minimum time interval between the "event-free" and the time of coronary incident, for which accurate data was found for each patient, was 5 months and the maximum 26 months (mean 13.1 ±6.6 months).

The total amount of iron administered varied from 0g to 25.6g, with a mean of 6.7g ±8.1g. The mean weekly dose, which is giving us an easier approach to the followed treatment, was 170mg ±120mg. The mean weekly dose during the time of each coronary incident was 130mg (min: 0 ; max: 300mg). Patients had a mean serum Fe concentration of 75.5mcg/dl ±55mcg/dl and a mean ferritin concentration of 711.7ng/ml ±610.6ng/ml. Their mean hematocrit was 36.2% ±3.1%, ranging from 32% to 42%.

Hematocrit level was found to have a strong correlation with serum iron concentration (Correlation Coefficient: 0.711 ; $p<0.001$) and with the total amount of administered iron (CC: 0.639 ; $p<0.038$), but was not found to be related to higher doses (300mg/week) of iron treatment. Additionally, both serum Fe (CC: 0.872 ; $p<0.001$) and ferritin (CC: 0.673 ; $p<0.023$) were strongly positively correlated with the total amount of administered iron. Ferritin was also found to be negatively correlated with the mean dose of rhEPO administered per week (CC: -0.645 ; $p<0.024$) and this correlation was proven even stronger when adjusted for relatively skewed values (CC: -0.681 ; $p<0.015$).

The mean rhEPO weekly dose administered 10500 ±4000 iu (rounded to the nearest 500) was found to be negatively related to the total amount of administered iron (CC: -0.597 ; $p<0.052$).

The mean WBC of the patients was 7294/μL ±2546/μL. In our study WBC was correlated positively with the duration of hemodialysis treatment (CC: 0.820; $p<0.001$). It is worthwhile to mention that WBC was also found to have a positive correlation with serum triglycerides concentration (CC: 0.566 ; $p<0.055$) and platelet count (CC: 0.629 ; $p<0.028$), but there was found no direct correlation between platelet count and angina pectoris incidence.

On the other hand platelet count was found to be positively correlated with the coronary events (CC: 0.591 ; $p<0.043$). Additionally platelet count was found positively correlated with the duration of the "intensive" iron treatment (CC: 0.56 ; $p<0.057$), but not with milder treatment.

Coronary incidents were also found to be dependent on age (CC: 0.605 ; $p<0.037$).

There was no significant correlation between coronary incidents and rhEPO, or between WBC and rhEPO as regards the mean weekly dose, or the total amount of rhEPO that each patient received. This result remained unchanged even after correction for relatively skewed data.

Finally, coronary events incidence was found strongly positively related to the duration of "intensive" iron administration (CC: 0.665 ; $p<0.018$). In order to test further the accuracy of this possible correlation, patients were divided in three different treatment-related periods. Comparisons among treatment periods were made using ANOVA. No significant correlation for treatment period 1 and treatment period 2 was found (F_1: 2.01 ; $p<0.191$ and F_2: 0.139 ; $p<0.934$ respectively). As regards treatment period 3, statistical analysis showed that the administration of 300mg of iron per week had a significant correlation with the incidence of coronary events (F_3: 4.47 ; $p<0.04$).

Discussion

The skepticism that rises from this study mainly concerns the safety and necessity of "intensive" iron treatment in coronary heart disease patients that are receiving hemodialysis treatment.

There are many different possible regimens of i.v. iron administration, from low doses given three times a week, to higher doses given once a week or every 15 days[15,16,18]. Iron sucrose has been shown to be safe even when administered in doses of 300mg i.v. over 2 hours[18]. Intense dosing of i.v. iron in hemodialysis patients was associated with an elevated risk of death or rate of hospitalization, even after adjusting for demographic and comorbidity characteristics[19]. Similar results were seen in non-uremic patients, where high serum iron levels and iron therapy were associated with a higher all cause death rate and a higher infectious cause death rate[20].

It seems that intravenous iron treatment which is commonly administered in rapid infusion rate, causes "oversaturation" of transferrin[16,21]. This effect was found to be dependent to transferrin levels[16]. Transferrin overasaturation is indicative of nontransferrin-bound iron (NTBI), which is circulating iron that is not tightly bound to transferrin[22]. Even relatively low doses of iron (100mg) often lead to transferrin oversaturation and to the presence of NTBI which is catalytically active and potentially toxic. This labile iron pool may promote bacterial growth[23]. Additional support to the later observation is conferred from the fact that polymorphonuclear leukocytes killing capacity decreases in response to high-dose parenteral iron[24].

Another detrimental effect of non-transferrin bound iron is represented by its ability to initiate oxidative reactions. The presence of even traces of iron salts can promote lipid peroxidation and the superoxide – dependent formation of hydroxyl radicals from hydrogen peroxide[25-27]. The initiation of this reactions can induce tubular and endothelial cell death[28,29] and

promote atherogenesis[30,31]. Intravenous administration of iron leads to increased lipid peroxidation in several tissues, including the liver, spleen, heart and adipose tissue, but its greatest effects concern plasma lipids[32]. Even a single dose of i.v. iron (100mg) can increase lipid oxidation[33], while rapid vs slow infusion doesn't seem to alter this effect[34]. The same dose regimen has been shown to increase oxygen radical stress and acute endothelial dysfunction[35]. Cumulative iron dose has been incriminated in the induction of atherosclerosis in ESRD patients[36].

Baseline serum ferritin levels are also correlated with oxidative stress. Higher baseline levels of serum ferritin associated with i.v. iron administration, lead to the exacerbation of the already increased oxidative stress found in uremic patients on hemodialysis[37]. Dosage and speed of administration has been reported to have a probable association with free iron generation and oxidative stress[38]. Oxidative stress in ESRD patients should be considered as a potentially important source of morbidity and mortality[39].

Many factors have been incriminated for the appearance of coronary heart disease in hemodialysis patients[2-6]. The correlation of age, white blood cell count, triglycerides, platelet count, duration of hemodialysis treatment and duration of "intensive" iron administration with the incidence of angina pectoris was investigated in this study. Various degrees of correlation were found among these factors in this subset of patients (Table 3).

Hematocrit level was not found to be associated with the incidence of angina pectoris in this subset of patients. It is common knowledge that lower Ht levels are linked with higher morbidity and mortality in ESRD patients and target Ht level is accepted to be between 33% and 36%[6,7]. Only two of the patients had Ht equal to 32%, with the rest of them having Ht $\geq$ 34%, this is most likely to be the explanation why there was found no link, in the present study, between Ht and the incidence of angina pectoris.

Hematocrit was found to be depended on serum Fe concentration and on the total amount of administered iron, but not on intensive iron dose regimen. Taking in consideration the fact that their mean ferritin was well above the minimum desired limits (only in two cases they were found to have serum ferritin<100ng/ml), we can assume that in relatively iron replete patients more intense iron treatment (300mg/week) does not offer a greater Ht elevation rate in comparison with lower doses (100 or 200mg/week). This observation, inevitably, questions the necessity of intensive iron supplementation in relatively iron replete patients. Additionally, the well-known guideline that mean rhEPO dosage and responsiveness to this therapy depends on iron administration was also confirmed. Both serum iron and ferritin levels were correlated with the total amount of administered iron. In general practice, we prescribe to our non-HD dependent anemic patients iron supplements per os, in relatively small doses for a longer period of time. Although such an approach to hemodialysis patients might not be appropriate, more conservative regimens (e.g. lower i.v. doses) for a longer period should be considered.

The mean dose of rhEPO was negatively related to the total amount of administered iron. This finding is in accordance with the international literature, here it is proven that i.v. iron administration leads to lower rhEPO requirements even in iron replete patients[10-13].

Administration of i.v. iron has been incriminated for the induction of atherogenesis and possibly of coronary heart disease, mainly through its effects on lipid peroxidation[25-33,35,36]. Nevertheless, direct association between iron administration and coronary heart disease was not found so far.

The correlation of age and platelet count with coronary events is also in accordance with a recent study[40], where mean platelet volume was found to be independent factor of coronary heart disease and significantly dependent on platelet count. They also found serum triglycerides concentration and age, among other factors to be independent risk factors of coronary heart disease.

To our knowledge, this is the first time that intensive intravenous iron treatment is correlated with a clinical setting of coronary disease. This relation seems even more probable, since it was confirmed only for the intensive iron administration, while there was no correlation as regards the lower dose regimens. Additionally only the "intensive" dose regimen was correlated with platelet count. Taking in consideration that both factors were independently related to the incidence of angina pectoris, a cause – effect relation is reasonably suspected. On the other hand, the correlation of angina pectoris incidence with other risk factors has also been confirmed in earlier studies[35, 36,40].

There is a number of limitations concerning our study. The number of patients included in the study and the number of coronary incidents were small (10 patients, 22 incidents), even though the duration of follow-up was long-term (157 months, mean: 13.1 $\pm$6.6). This problem can be overcome in a larger, prospective study. There is no comparison with a similar group of "non-coronary" patients, but such a comparison was not within the objectives of our study, since the same group of patients followed three different dose regimens. Although white blood cell count represent a well-known risk factor of cardiovascular disease[41-44], we could not retrieve information from the medical files regarding the neutrophil count and lymphocyte count, which seem to be related to this process. This clinical aspect, possibly associated to oxidative stress, could also be investigated in a prospective study.

In conclusion, a significant association between intensive intravenous iron administration and the incidence of angina pectoris in stable coronary heart disease patients receiving hemodialysis treatment was found in this study.

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