Intravenous iron supplementation for correcting renal anemia in hemodialysis patients – critical approach to current practices based on single-centre experience

Suplementacja żelaza drogą dożylną w niedokrwistości nerkowopochodnej u pacjentów dializowanych – krytyczna ocena obecnej praktyki klinicznej w doświadczeniach jednego ośrodka

Summary

Intravenous iron, the procedure of choice to replete iron stores in hemodialysis patients can induce oxidative stress if the amount of “free” iron infused exceeds the capability of transferrin to bind it. TSAT increases significantly after both, iron saccharate and LMW-dextran in a dose-dependent manner. The retrospective study was undertaken to evaluate the maximum safe doses of both iv iron formulations and to design a protocol for iron repletion with minimum risk of “oversaturating” plasma transferrin. The 100 mg of LMW iron dextran proved safe in this regard in all patients, but the maximal safe doses in severe iron depletion were 50 mg and 200 mg for iron saccharate and LMW iron dextran 200 mg , respectively. Based on the observations a protocol for single dose iron amount and dose-interval was proposed. The literature review to support the rationale to avoid transferrin oversaturation with intravenous iron was also presented.

Key words: iron, renal failure, hemodialysis, renal anemia, transferrin saturation

Streszczenie

Dożylnie podawanie preparatów żelaza, procedura z wyboru dla uzupełnienia niedoborów żelaza u pacjentów hemodializowanych, może powodować stres oksydacyjny jeśli ilość podanego „wolnego” żelaza przekroczy zdolność wiązania go przez osoczową transferynę. TSAT rośnie znacząco, i proporcjonalnie do podanej dawki, po dożylnym podaniu żelaza – zarówno cukruzan, jaki niskocząsteczkowego dekstranu. Przeprowadzone przez nas badanie retrospektywne miało na celu określenie takich maksymalnych dawek każdego z preparatów, które niosą minimalne ryzyko „przesycenia” osoczowej transferyny, oraz zaproponowanie na tej podstawie protokołu bezpiecznego, pod tym względem, podawania żelaza. Dawka 100 mg niskocząsteczkowego dekstranu żelaza okazała się bezpieczna we wszystkich sytuacjach niedoboru żelaza, ale dawki 200 mg dekstranu żelaza i 50 mg cukruzan żelaza były bezpieczne tylko u pacjentów z dużym jego niedoborem. Na podstawie analizy wyników leczenia zaproponowano protokół wielkości i częstości dawkowania każdego z preparatów żelaza, oparty na aktualnych wynikach TSAT i osoczowej ferrytyny. Przedstawiono także przegląd piśmiennictwa uzasadniający konieczność dożylej suplementacji żelaza u pacjentów hemodializowanych i unikania powtarzanego przesycania transferyny.

Słowa kluczowe: żelazo, niewydolność nerek, hemodializa, niedokrwistość nerkowo pochodna, wysycenie transferyny

INTRODUCTION

In patients on hemodialysis due to the chronic renal failure the yearly loses of iron can exceed 3.0 g, which is 4-10 times more as compared to healthy population (1). The increased iron losses resulting from:
– intrahemodialyser clotting,
– postdialysis bleeding from needle insertion site,
– the incomplete blood return at cessation of the procedure,
– extensive laboratory examinations required to follow and treat hemodialysed patients,
– occult gastrointestinal bleeding,
can add 6-7 mg, or even more, to the physiological daily iron losses of 1-2 mg. The occult blood losses
and the need for blood sampling are responsible for the iron deficiency anemia present in 25% of patients commencing chronic dialysis treatment (2).

In healthy individuals the increased iron losses result in increased reabsorption of dietary iron, increased synthesis and release of transferrin, decreased synthesis of hepcidin, and, if anemia ensues, in increased erythropoietin synthesis. All these mechanisms are affected by renal insufficiency.

Advanced chronic renal disease results in inadequately low erythropoietin synthesis and excretion, and the resistance of erythroid progenitor cells to erythropoietin. Hemodialysis corrects these abnormalities in part only.

Iron and erythropoiesis in renal failure patients

Erythropoietin is critical for survival of erythroid progenitor cells before they differentiate into proerythroblast. Hypoerythropoietinemia, relative or absolute, causes apoptosis of burst-forming units-erythroid (BFU-E) and colony-forming units-erythroid (CFU-E) (3, 4). At the proerythroblast stage of erythropoiesis the cell becomes erythropoietin independent, and starts synthesis of alpha and beta hemoglobin chains. Shortly after, within few hours, large amounts of iron are taken up for hemoglobin synthesis, which is preceded by the presentation of transferrin receptors on the cell surface. The erythroblast iron uptake accelerates for 16 hours, several hours after the commencement of hemoglobin synthesis. In 24-30 hours the iron in-flow stops, and the synthesis of all hemoglobin inside the erythroblast is completed within 2.5 days (5).

The erythroblast infowing iron is stored initially inside ferritin capsules. The maturation of erythroblasts is reflected in staining – from the basophilic to polychromatophilic and, finally, to orthochromatophilic erythroblast. As a result, after 5 days and 4 further divisions, each proerythroblast produces 32 reticulocytes, which are released into the bloodstream. The reticulocyte is the first nonnuclear cell of erythroid, and after 24 hours matures to erythrocyte, which stays in blood for the consecutive 120 days, before erythroptosis eliminates it from circulating.

Clearly, adequate and timely availability of erythropoietin and iron to pre-orthochromatophilic erythroblast cells is crucial to prevent renal anemia. The inadequately low levels of endogenous erythropoietin can be easily increased using commercially available erythropoiesis stimulating agents (ESA).

The increased iron losses in CKD patients can be hardly replaced by diet for the increased levels of hepcidin in renal failure reduce the duodenal cells’ capability to release dietary iron into the blood stream. Calcium-based phosphate binders given orally to almost every renal patient, with an intention to decrease phosphate reabsorption, compete with iron for the divalent ion transporter on duodenal cells and further decrease dietary iron availability. Additionally, the need in renal patients to decrease dietary phosphate and avoid abundant protein load, often results in diminished delivery of heme iron in meat. All these factors taken together in renal patients – the reduced uptake of dietary iron to the duodenal cells and the inhibition of releasing the reabsorbed iron from duodenal cells into blood contribute to iron depletion.

It is unclear if the hyperhepcidinemia in CKD patients results from abnormal synthesis, decreased degradation by remnant renal tissue, or both. The uremia-related inflammation seems to stimulate hepcidin synthesis, which in turn, like in duodenal cells, limits iron release form ferritin-reach macrophages and reticuloendothelial cells. Thus, even in the iron repleted renal patients, the availability of iron for erythropoiesis can be limited (relative or functional iron deficiency), particularly when ESAs are given.

Absolute and functional iron deficiency in renal patients

The absolute iron deficiency is diagnosed in patients presenting iron-deficient erythropoiesis. Reduced hemoglobin concentration, plasma ferritin and iron concentrations, transferrin saturation, mean erythrocyte hemoglobin content and volume (MCH and MCV), mean reticulocyte hemoglobin content (CHR) and percentage of hypocromic erythrocytes are commonly used to evaluate iron stores and its availability to erythropoiesis. Should hemoglobin concentration increase after the iron have been supplemented in patient with apparently normal erythrocytosis, the functional iron deficiency is diagnosed.

The normal erythropoiesis produces erythrocytes and reticulocytes containing more hemoglobin (CHR and MHC, respectively) than 28 pg/cell (normal value 28-32 pg/cell). The percentage of hemoglobin depleted erythrocytes (hypochromic erythrocytes) – %HRC is lower than 2% in normal population and should be kept < 5% in renal patients. Higher values of %HRC are suggestive of iron-deficient erythropoiesis. Plasma ferritin, fragments of protein capsules storing intracellular inorganic iron, reflects the amount of iron released from the apoptotic and necrotic cells. Thus, decreased plasma ferritin concentration always indicate absolute iron depletion. The absolute iron deficiency is diagnosed in renal patients after plasma ferritin fell below 225 pmols/l (100 ng/ml) in patients free from dialysis, and below 450 pmol/l (200 ng/ml) in patients on chronic hemodialysis.

The increased ferritin levels can be indicative of iron overload, inflammation (ferritin is a member of acute-phase proteins family), or both. For uremia induces systemic inflammation, ferritin concentrations normal at healthy population, in renal failure can be observed despite severe iron depletion. This is why normal iron status in renal failure can be expected at values higher than in general population, particularly when other acute phase indicators are also high. Even ferritin levels as high as > 1123 pmol/ml (500 ng/ml) cannot warrant iron repletion in renal patients (6).
The basophilic erythroblast takes-up iron from two sources – iron-loaded macrophages forming the center of the intramedullary erythroblastic island and from plasma iron transporter – transferrin, which is produced by the liver. Inflammation and malnutrition reduce transferrin levels, which makes it as good risk factor for increased mortality as the albumin concentration (7)

The diagnosis of functional iron deficiency can be made only ex juvantibus, i.e. when iron supplementation increases hemoglobin concentration. This happens when the release of iron stores is insufficient to support normal erythropoiesis, and can be reflected, at more advanced stages by low transferrin saturation (TSAT). Levels of TSAT < 20% are suggestive of iron functional depletion, irrespective of ferritin concentration. This has been challenged by the results of DRIVE study – patients presented with apparently repleted iron stores had iron-restricted erythropoiesis reversed after additional iron supplemented intravenously (8, 9).

Thus, each renal patient presenting iron-restricted erythropoiesis (overt anemia, increased percentage of hypochromic reticulocytes and/or erythrocytes, high transferrin (overt anemia, increased percentage of hypochromic reticulocytes and/or erythrocytes, high demand for ESAs) should be offered some form of iron supplementation, irrespective of being on hemodialysis.

IRON SUPPLEMENTATION

With no doubt intravenous iron is superior to oral in hemodialysis patients. This is less evident in predialysis and peritoneal dialysis patients. The upper limits of iron-metabolism parameters indicative of stopping the supplementation are not known. Neither the frequency or amount of single dose are internationally agreed upon. This is why every physician and every dialysis unit are advised to design their own strategy reflecting the general guidelines.

The most popular nowadays intravenous iron formulation are:
- Iron saccharate (Venofer),
- Iron gluconate,
- Low molecular dextran iron (CosmoFer).

The clinical use of high molecular weight (HMW) iron dextran is disadvised for the risk of serious anaphylactic reactions is high. The side effects of low molecular weight (LMW) iron dextran are less frequent as compared to HMW iron dextran. These are even less frequent and serious as compared to the observed after saccharate (10, 11) or gluconate base formulations (12). Even so, the test dose of LMW iron is required prior to each infusion, for the patient could carry preformed anti-dextran antibodies (13).

The iv iron is usually well tolerated, unless given at high dose and rate. There are no data the repeated iv iron is harmful as regards to cancer or accelerated atherosclerosis, even if single doses of 100 mg iron sucrose (IS) iv increase plasma TSAT after 210 min to more than 80% (14), and cause proteinuria and albuminuria shortly after the medication was given (15). The effect is thought to result from the presence of highly toxic free iron in the solution infused (16,17).

THE FREE IRON AND TISSUE DAMAGE

The iv iron formulations contain two forms of iron – the “bound” and the “free” iron. The differences is in size of the particle determine the “free” iron content – the smaller the particle the more “free” iron. The “bound” iron is taken-up by macrophages, and other cells, by pinocytosis. The “free” (“unbound”) iron, if not buffered by transferrin can damage tissue.

The “free” iron particles are smaller as compared to “bound” and are easy available to tissue components. Transferrin, the plasma iron transporter binds “free” iron till saturated. However the TSAT values close to 100% indicate that free iron cannot be buffered and the tissue damage can result. There is a clear correlation between the molecular weight of iron formulation and the content of “unbound” iron. The saturation of transferrin with the infused “free” iron is not immediate – it takes up to 210 min, before the maximum TSAT value is reached (10). This is why, as a routine we determine TSAT prior to and 210 min after the infusion of iv iron.

Based on the data available from the literature one can conclude that:
- Iron supplementation is crucial to anemia control in hemodialysis patients, and iron repletion should precede ESAs therapy.
- Two separate protocols – iron store repletion and iron store maintenance – are usually needed, but the time interval nor the maximum single iron dose are not known.
- The TSAT should never reach values close to 100%, and probably should not exceed 50%, at least for longer time-period.
- There are no data in hemodialysis patients on TSAT values after the standard iron dose of 50 or 100 mg is given iv.

Since there are no published data on the lagging TSAT levels following single iron iv infusion, we considered it interesting to verify, retrospectively, the impression we have had, the routine iron maintenance and repletion doses did not oversaturate transferrin, was justified. We were also curious to find, if any relation existed between the pre-dosing ferritin level and post-dosing transferrin reserves, expressed as TSAT. Finally we wanted to check, if the iron LMW dextran doses
could have been higher as compared to iron saccharate, and if one protocol for anemia management could be designed. The highest iron doses acceptable at our unit are 200 mg for LMW dextran and 50 mg for iron saccharate to avoid the lagging transferrin oversaturation phenomenon described by (10, 11).

AIM

To design, based on retrospective data from our unit, a protocol for safe dosing of iron dextran (LMV-Id) and iron saccharate (IS) – CosmoFer and Venofer, respectively, to replete and maintain iron stores in dialysis patients.

MATERIALS AND METHODS

This retrospective study was done in 4 groups of stable, adult HD patients, 8 people each – 200I, 100I, 50I, and NoI, receiving single iron dose, as the routine anemia therapy, of 200mg LMW-ID; 100 mg LMW-ID, 50 mg IS and no iron at all, respectively. Patient were selected from the small cohort of 112 hemodialysis patients at our dialysis unit, who received the treatment for at least three months. In all selected patients the variation in hemoglobin concentration has been lower than 1.0 g/dl during the last three months preceding inclusion into the study. Patients with different length of dialysis sessions and who changed epoetin weekly doses in last two months were not eligible to the study.

The iron was given as a short iv infusion at the 30th min. of the standard 240 min long HD session. At the beginning and at the end of HD (i.e. 210 min. after the infusion commenceent) the plasma Fe, TIBC, ferritin (F), transferrin (TF), alanine and aspartate transferases (ALT and AST, respectively) were measured, and the TSAT calculated.

STATISTICS

The data are presented as mean ± standard deviation from the mean (Xmean ± SD). The normal distribution was evaluated using Fisher’s test, and the differences between the variables of normal distribution were calculated using the Student’s t-test. For other variables the Mann Whitney U test and the Wilcoxon-Cox test were used to evaluate the significance of difference between the means. All tests were performed using EpilInfo 3.5.2 software (freeware from the Centres for Disease Control and Prevention, US).

RESULTS

The predialysis hemoglobin concentrations, AlaT, nor AspaT activity differed significantly between the groups. Iron infusion increased AlaT and Aspat in I50 and I100, but not in NoI and I200 groups. All post dialysis aminotransferase activity values remined within the normal levels (tab. 1).

The pre- and postdialysis values of parameter reflecting iron plasma content and transfer are presented in table 2.

The pre-dose ferritin levels were significantly lower in 200I, 100I and 50I as compared to NoI, and there was no difference between the 100I, 200I and 50I groups.

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>No Iron (bez żelaza iv)</td>
<td>Pre 11.5 ± 1.4</td>
<td>15.5 ± 19.2</td>
<td>16.4 ± 12.2</td>
<td>222.6 ± 78.0</td>
</tr>
<tr>
<td></td>
<td>Post 18.63 ± 19.52</td>
<td>19.38 ± 14.13#</td>
<td>21.1 ± 14.13#</td>
<td>241.6 ± 70.1</td>
</tr>
<tr>
<td>50 mg Iron Sucrose (50 mg cukrzuzu żelaza)</td>
<td>Pre 11.3 ± 1.5</td>
<td>16.8 ± 6.8</td>
<td>16.0 ± 6.7</td>
<td>221.1 ± 38.1</td>
</tr>
<tr>
<td></td>
<td>Post 20.00 ± 8.32#</td>
<td>21.00 ± 8.05#</td>
<td>254.2 ± 47.5#</td>
<td></td>
</tr>
<tr>
<td>100 mg Iron Dextran-LMW (100 mg dekstranu żelaza)</td>
<td>Pre 10.7 ± 1.2</td>
<td>15.7 ± 7.1</td>
<td>15.4 ± 3.8</td>
<td>231.6 ± 28.4</td>
</tr>
<tr>
<td></td>
<td>Post 17.86 ± 7.76†</td>
<td>21.43 ± 5.68#</td>
<td>297.7 ± 18.8#</td>
<td></td>
</tr>
<tr>
<td>200 mg Iron Dextran- LMW (200 mg dekstranu żelaza)</td>
<td>Pre 10.3 ± 1.2</td>
<td>10.2 ± 2.9</td>
<td>12.5 ± 4.1</td>
<td>225.8 ± 45.5</td>
</tr>
<tr>
<td></td>
<td>Post 10.63 ± 2.83</td>
<td>15.00 ± 3.93</td>
<td>277.7 ± 55.2*</td>
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</tr>
</tbody>
</table>

Post vs pre: #p < 0.05; †p < 0.01; *p < 0.001

Table 1. Pre- and postdialysis (lagged post iron) values of hemoglobin concentration, alanine and aspartate aminotransferases activity, and total iron binding capacity (TIBC).

<table>
<thead>
<tr>
<th>GROUP/Param</th>
<th>Fe(pre) [µg/dl]</th>
<th>Ferritin(pre) [ng/ml]</th>
<th>TSAT(pre) [%]</th>
<th>TSAT(post) [%]</th>
<th>dTSAT [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Iron</td>
<td>64.3 ± 41.8</td>
<td>977.2 ± 375.8</td>
<td>28.0 ± 15.8</td>
<td>26.3 ± 15.0</td>
<td>-1.7 ± 3.37</td>
</tr>
<tr>
<td>50 mg Iron Sucrose</td>
<td>41.1 ± 15.4</td>
<td>573.9 ± 92.6*</td>
<td>19.0 ± 5.6</td>
<td>38.6 ± 7.0*#</td>
<td>19.6 ± 4.8*#</td>
</tr>
<tr>
<td>100 mg Iron Dextran-LMW</td>
<td>53.3 ± 13.6</td>
<td>476.0 ± 217.5*</td>
<td>23.0 ± 5.2</td>
<td>32 ± 5.6</td>
<td>9.2 ± 2.6*</td>
</tr>
<tr>
<td>200 mg Iron Dextran- LMW</td>
<td>41.3 ± 22.5</td>
<td>466.7 ± 210.1*</td>
<td>18.4 ± 9.6</td>
<td>46.8 ± 15.4*</td>
<td>28.5 ± 21.4*</td>
</tr>
</tbody>
</table>

*different from NoI, †different from 100I; pre = prior to hemodialysis session; post = at the end of hemodialysis swwssion; dTSAT = difference between the post and pre TSAT values.
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The ferritin concentration increased significantly only in 50I group-by 123.5 ± 55.6 ng/ml (p < 0.001) to reach 697.4 ± 87.6 ng/ml. In the remaining three groups – two receiving LMW-ID and one receiving no iron, the ferritin level remained stable. No other pre-dose parameters measured did differ between the groups.

Following the infusion, TSAT did not change in NoI, and significantly increased in all three groups receiving iv iron, i.e. 50I, 100I and 200I. The increase in TSAT was significantly higher in 50I and 200 I as compared to 100I. The maximum increase in TSAT was 27.1% in 50I, 12.6% in 100I, and 56.2% in 200I. The maximum TSAT level reached 51.6% in 50I, 38.4% in 100I, and 72.4% in 200I. The increases in plasma ferritin and TSAT correlated positively with the predosing values. Only the changes of TSAT were influenced by the dose and formulation of iron – the lowest increases were observed in 100I group.

Following the analysis a model of the single dose amount and time-interval between the two consecutive doses was designed, which is presented in Tables 3 and 4, respectively.

DISCUSSION
In all three “intervention” groups iron was given during the first hour of dialysis session, for we hoped to remove “free” iron and keep in blood the “bound” iron. It is well known, the clearance of “bound” iron is negligible (< 25 ml/min in vitro) (18, 19).

Intravenous iron during hemodialysis increased TSAT in each group, which was not observed in patients not receiving iron. This strongly suggests causal relation between intervention and the decrease in transferrin iron binding capacity reflected by decreased the retrospective design of our intervention study slightly limits the validity of conclusions drawn – the intervention is clear and the changes following the intervention can be compared to the no-intervention (“control”) group, as in prospective studies. However, the “control” group differed slightly from “intervention” groups in that patients were able to keep adequate hemoglobin concentration without iron substitution. The higher concentrations of ferritin in the “control” group most probably reflects more repleted iron stores as compared to “intervention” groups. This could also indicate, the higher ferritin concentrations could be a new target for anemia correction in dialysis patients, which has been already suggested (20).

Higher standard iron doses were given to patients with lower ferritin and hemoglobin levels – the correlation was not statistically significant due to large dispersion of results in each group. This observation reflects rather our intuitive anemia control practices than poor qualification into the study. Taking the above limitations into consideration, a prospective study, with larger cohorts and narrower inclusion criteria would be of value.

The hemodialysis procedure increased, slightly but statistically significantly, the AspA activity, which has not been further increased by iron infusion. The AlaT activity also increased slightly in all groups, but significantly only in IS0 and II00 groups. These findings indicate, that iron infusion did not have significant impact on aminotransferase activity.

The plasma ferritin concentration increased only in IS0, but did not change during hemodialysis in II00, 1200 nor the NoI (“control”) group. This was the only group, where iron saccharate was given. Since ferritin reflects either increased cytolysis or increased intracellular ferritin and iron content, one can assume that iron saccharate infusion, even in small doses resulted in tissue damage, which has been already previously described by others (10, 13, 16). However, this study

<table>
<thead>
<tr>
<th>Ferritin</th>
<th>TSAT &lt; 20%</th>
<th>20-30%</th>
<th>30-50%</th>
<th>&gt; 50%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;600 ng/ml</td>
<td>100 D</td>
<td>100 D</td>
<td>100 D</td>
<td>0</td>
</tr>
<tr>
<td>200-600 ng/ml</td>
<td>100 D</td>
<td>100 D</td>
<td>100 D</td>
<td>0</td>
</tr>
<tr>
<td>&lt; 200 ng/ml</td>
<td>200 D</td>
<td>100 D</td>
<td>100 D</td>
<td>0</td>
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Table 3. The suggested maximal single dose of intravenous iron LMW and sucrose.

<table>
<thead>
<tr>
<th>Ferritin</th>
<th>TSAT &lt; 20%</th>
<th>20-30%</th>
<th>30-50%</th>
<th>&gt; 50%</th>
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<tr>
<td>&gt; 800 ng/ml</td>
<td>90?</td>
<td>90?</td>
<td>90?</td>
<td>90?</td>
</tr>
<tr>
<td>500-800 ng/ml</td>
<td>28?</td>
<td>90?</td>
<td>90?</td>
<td>90?</td>
</tr>
<tr>
<td>200-500 ng/ml</td>
<td>14</td>
<td>28</td>
<td>28</td>
<td>90?</td>
</tr>
<tr>
<td>&lt; 200 ng/ml</td>
<td>7</td>
<td>14</td>
<td>28</td>
<td>28</td>
</tr>
</tbody>
</table>

Table 4. The suggested time-span (in days) between iron doses in hemodialysed patients based on actual ferritin and TSAT levels.

? – re-evaluate before dosing.
seems to suggest, that even doses of iron saccharate as small as 50 mg could result in tissue damage.

The iron infusion increased significantly plasma iron, TSAT and TIBC, an effect not caused by hemodialysis only. The increasing TSAT means a decreasing capacity of transferrin to bind “free” iron. This increase was only. The increasing TSAT means a decreasing capacity and TIBC, an effect not caused by hemodialysis.

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CONCLUSIONS

This retrospective analysis of our data and literature review suggest that iron saccharate (Venofer) 50 mg iv does not oversaturate transferrin in iron depleted hemodialysed patients, but higher doses given as single infusion should be avoided. Iron low molecular dextran (Cosmofer) can be given in doses not exceeding 200 mg/per infusion, but only in severely iron depleted hemodialysis patients. The 100 mg of iron LMW dextran can be safely given at various time intervals to all hemodialysis patients till iron repletion is achieved, and subsequently to maintain it. The protocol of iron dose amount and interval we propose, could help avoiding the consequences of repeated oxidative stress second to free iron exposure resulting from iron overdosing.

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