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Dialysate iron therapy: Infusion of soluble ferric pyrophosphate via the dialysate during hemodialysis

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Dialysate iron therapy: Infusion of soluble ferric pyrophosphate via the dialysate during hemodialysis.

Background. Soluble iron salts are toxic for parenteral administration because free iron catalyzes free radical generation. Pyrophosphate strongly complexes iron and enhances iron transport between transferrin, ferritin, and tissues. Hemodialysis patients need iron to replenish ongoing losses. We evaluated the short-term safety and efficacy of infusing soluble ferric pyrophosphate by dialysate.

Methods. Maintenance hemodialysis patients receiving erythropoietin were stabilized on regular doses of intravenous (i.v.) iron dextran after oral iron supplements were discontinued. During the treatment phase, 10 patients received ferric pyrophosphate via hemodialysis as monthly dialysate iron concentrations were progressively increased from 2, 4, 8, to 12 μg/dl and were then sustained for two additional months at 12 μg/dl (dialysate iron group); 11 control patients were continued on i.v. iron dextran (i.v. iron group).

Results. Hemoglobin, serum iron parameters, and the erythropoietin dose did not change significantly from month 0 to month 6, both within and between the two groups. The weekly dose of i.v. iron (mean ± SD) needed to maintain iron balance during month 6 was 56 ± 37 mg in the i.v. iron group compared with 10 ± 23 mg in the dialysate iron group ($P = 0.001$). Intravenous iron was required by all 11 patients in the i.v. iron group compared with only 2 of the 10 patients receiving 12 μg/dl dialysate iron. The incidence of adverse effects was similar in both groups.

Conclusions. Slow infusion of soluble iron pyrophosphate by hemodialysis may be a safe and effective alternative to the i.v. administration of colloidal iron dextran in maintenance hemodialysis patients.

Iron deficiency is the most common nutritional problem worldwide, causing iron-deficiency anemia in 500 to 600 million people [1, 2]. Iron deficiency is associated with prematurity and low birth weight during pregnancy, defects in cognitive and psychomotor development during childhood, and impaired work capacity in adulthood [3–8]. Oral iron supplementation programs have failed primarily because of noncompliance in addition to gastrointestinal adverse effects [9]. As an adjunct or alternative to the oral route, iron has been administered parenterally for more than 100 years [10]. Soluble iron compounds are considered too toxic for parenteral administration, as ionization of soluble iron salts liberates free iron, which catalyzes free radical formation and lipid peroxidation [11, 12]. The colloidal iron compounds used for parenteral administration such as iron dextran, saccharate, or gluconate are also associated with serious side-effects, including hypotension and anaphylactoid reactions [13]. The toxicity of these compounds may be secondary to liberation of free iron caused by chemical interactions in plasma [13] or circulating antidextran antibodies in patients administered repeated doses of iron dextran [14]. Ferric iron is strongly complexed by pyrophosphate; the log of stability or formation constant (Kstab) is 22.2 [15]. Pyrophosphate is known to trigger iron removal from transferrin, enhance iron transfer from transferrin to ferritin, and promote iron exchange between transferrin molecules [16–19]. These properties suggest that ferric pyrophosphate may be suitable for parenteral administration. Furthermore, ferric pyrophosphate (molecular weight of 745.2) is soluble in water when the granules have been prepared by chemical reaction with citric acid and sodium hydroxide.

A majority of maintenance hemodialysis patients treated with erythropoietin become iron deficient and need i.v. iron supplementation to maintain optimal iron balance [20]. In hemodialysis patients, small water-soluble molecules can be directly infused into the circulation by their addition to the dialysate solution [21]. We have previously demonstrated that ferric pyrophosphate is transported from the dialysate to the blood compartment during simulated, *in vitro* hemodialysis (A. Gupta, un-

Key words: dialysis, iron supplementation, renal toxicity, colloidal iron dextran, erythropoietin, anemia.

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published data). The goal of this study was to determine whether infusion of soluble ferric pyrophosphate by dialysis (dialysate iron therapy) is safe and could obviate the need for oral and intravenous (i.v.) iron in maintenance hemodialysis patients.

METHODS

Study design

Informed consent was obtained from 24 patients with end-stage renal disease receiving maintenance hemodialysis for at least three months. The experimental therapy of ferric pyrophosphate administration by hemodialysis was compared with the recommended practice of maintenance i.v. iron dextran treatment [20] in this open-label, single-center clinical study. The study was approved under an Investigational New Drug Application by the United States Food and Drug Administration and by the Human Rights Committee at Henry Ford Hospital (Detroit, MI, USA).

The inclusion criteria for the study were as follows: male and female patients 18 years of age or older undergoing hemodialysis three times a week and receiving erythropoietin for the treatment of anemia, transferrin saturation (TSAT) between 18 and 25% and serum ferritin level between 100 and 200 μg/liter, and a need for parenteral iron supplementation within a three-month period prior to enrollment. Patients were excluded if they maintained adequate iron balance (TSAT more than 25% and serum ferritin more than 200 μg/liter) without parenteral iron supplementation or had severe iron deficiency (TSAT less than 15% and/or serum ferritin less than 50 μg/liter), had a history of clinically significant allergic reaction to iron, had a history of drug or alcohol abuse within six months prior to enrollment, had a history of hepatitis B or HIV infection, or were child-bearing females not willing to use effective birth control measures.

The study was performed in two phases, a pretreatment (month 0) phase of four weeks, followed by a treatment phase (month 1 to 6) of 24 weeks. Predialysis hemoglobin, hematocrit, serum iron, total iron-binding capacity (TIBC), and ferritin were measured every week throughout the study. Erythropoietin was administered intravenously up to three times per week during hemodialysis, and the dose was adjusted every four weeks in order to maintain hemoglobin levels between 10 and 12 g/dl. Starting in month 0 and during the seven-month study period, patients were instructed not to take any oral iron supplements. Throughout the study, all patients were eligible to receive variable maintenance doses (0, 25, 50, or 100 mg) of supplemental i.v. iron dextran (INFeD®; Schein Pharmaceutical, Inc., Florham Park, NJ, USA) once a week during hemodialysis in order to maintain a predialysis TSAT of more than 20% and ferritin of more than 100 μg/liter. In all patients, overt iron deficiency (TSAT less than 20%) was treated with 100 to 200 mg of iron dextran i.v. with each hemodialysis session, up to a total dose of 400 to 1000 mg at the discretion of the principal investigator (A.G.). The serum iron parameters in the last two weeks of the pretreatment phase were used for comparison with the parameters in the treatment phase. During the treatment phase, a cohort of patients was assigned to receive iron pyrophosphate in an escalating dose via the dialysate (dialysate iron group) during every hemodialysis session for a total of 24 weeks, whereas a control group continued to receive i.v. iron alone (i.v. iron group). If TSAT exceeded 50%, maintenance i.v. and/or dialysate iron supplementation were discontinued.

During the pretreatment phase, one patient died and one patient was transferred to another dialysis facility. During the treatment phase, one patient from the dialysate iron group withdrew after only one dialysis session because of lack of interest. Thus, data are reported on the 21 patients who completed the study.

Hemodialysis with solutions containing ferric pyrophosphate

Ferric pyrophosphate complexed with sodium citrate is soluble in aqueous solutions (ferric pyrophosphate soluble; Mallinckrodt Inc., St. Louis, MO, USA) [22]. Soluble ferric pyrophosphate was dissolved in purified water, and this solution was added to a freshly prepared bicarbonate concentrate solution. Dialysate solutions containing the desired concentration of soluble ferric pyrophosphate were generated by the addition of an appropriately higher concentration of the compound to the bicarbonate concentrate. A stable and clear dialysate solution containing up to 71 μg/dl iron as ferric pyrophosphate could be generated using this method. Bicarbonate concentrate solutions were used within 24 hours of preparation to avoid bacterial growth. Based on previous *in vitro* hemodialysis studies using dialysate iron concentrations between 2 and 70 μg/dl (A. Gupta, unpublished data) and taking patients' safety into consideration, in our study, an initial dialysate iron concentration of 2 μg/dl was increased every four weeks to 4, 8, and then to a maximum of 12 μg/dl, which was then sustained for two additional months. All patients were dialyzed using polysulfone membrane filters (F-80® or F-8®; Fresenius USA, Walnut Creek, CA, USA), and the filters were reused after heat sterilization. The hemodialysis-related parameters (mean ± SE) were as follows: dialysate flow rate, 800 ml/min; blood flow rate, 465.1 ± 14.43 ml/min; dialysis time, 217.5 ± 8.1 min; and KT/V, 1.53 ± 0.13.

Efficacy parameters

Hemoglobin and hematocrit were measured weekly by a colorimetric method, and the mean corpuscular

hemoglobin content of reticulocytes (reticulocyte hemoglobin) was measured at the end of each month using a flow cytometry method (H-3; Bayer Diagnostics, Tarrytown, NY, USA). Testing for reticulocyte hemoglobin was not available during months 0 and 1. Serum iron, TIBC, and ferritin were measured weekly. Serum iron and TIBC were analyzed by a colorimetric method (Hitachi 747; Boehringer Mannheim Corp., Indianapolis, IN, USA). Ferritin was analyzed by a chemiluminescent immunoassay method (ACCESS; Beckman Instruments, Fullerton, CA, USA) until the end of month 4. The heterogeneous competitive magnetic separation assay (HCMSA) using Immuno-1 (Bayer Diagnostics) was used for the determination of ferritin for the remaining samples of the study. The two methods give similar values when compared using the "College of American Pathologists" (CAP) surveys (Dr. James Zazra, Lifechem Laboratories Inc., Rockleigh, NJ, USA, personal communication). TSAT was calculated as follows:

$$\text{TSAT (\%)} = [\text{serum iron (}\mu\text{g/dl)/TIBC (}\mu\text{g/dl)}] \times 100$$

Safety parameters

Nutritional status was monitored by recording body weight at every dialysis session and by monthly serum albumin, cholesterol, and triglyceride measurements. Because there is a theoretical risk of ferric pyrophosphate causing hyperphosphatemia and chelation of serum calcium leading to hypocalcemia, serum calcium and phosphorus were monitored monthly. Serum ferritin was measured weekly to detect iron overload, defined as ferritin greater than 800 μg/liter. Patients were closely monitored to detect signs and symptoms of iron toxicity (malaise, headache, back pain, flushing, myalgia, arthralgia, vomiting, diarrhea, urticaria, hypotension, respiratory distress, anaphylactoid reactions, and lymphadenopathy).

Statistical analysis

For each study variable, monthly averages and changes from pretreatment (month 0) to the final observation period (month 6) were compared between the two groups by *t*-test or Wilcoxon rank sum test. The changes from pretreatment to month 6 were also tested within each group by paired *t*-test or Wilcoxon signed rank test. Analysis was performed using the SAS procedures TTEST, MEANS, UNIVARIATE and NPAR1WAY [23]. Sample size was based on the anticipation that a 50% decrease in maintenance iron requirements could be detected. All results are reported as mean ± SD unless otherwise stated, with a P of less than 0.05 considered statistically significant.

RESULTS

From November 1996 to July 1997, a total of 21 hemodialysis patients were followed. Demographic and concomitant disease states of the patients are shown in Table 1. The predominance of African Americans was consistent with the demographics of our dialysis population. The efficacy parameters are shown in Table 2, whereas the safety parameters are summarized in Table 3. None of these variables were statistically different between the two groups during month 0. Furthermore, there were no significant differences in hemodialysis prescription or dialysis adequacy between the two groups in the baseline or the treatment phase (data not shown).

Table 1. Characteristics of patients included in the final analysis

Characteristic	Dialysate iron	i.v. iron
N	10	11
Gender (male)[a]	6 (60%)	7 (64%)
Age (years)[b]	53.5 ± 14.3 (32–82)	58.1 ± 1.5 (32–76)
Race (African American)[a]	9 (90%)	11 (100%)
Hypertension[a]	10 (100%)	11 (100%)
Diabetes mellitus[a]	6 (60%)	7 (64%)

[a] Indicates patients with the characteristic; number in parentheses indicates percent of patients in the group

[b] Plus-minus values are means ± SD, age range is shown in parentheses

Efficacy parameters

Whole blood hemoglobin was maintained at a stable target level in both the groups, without any significant difference in between the groups (Table 2 and Fig. 1A). There was no significant change in erythropoietin dose throughout the study in either group and no significant difference between the two groups (Table 2 and Fig. 1B). The dose of erythropoietin was increased from 1000 to 4000 units per treatment in the final month for a patient in the dialysate iron group, when the hemoglobin declined following an arterial bypass procedure. This led to an abrupt increase in the mean erythropoietin dose for the dialysate iron group in the final month of the study.

Patients in both groups were prescribed 0 to 200 mg i.v. iron per dialysis session, up to a maximum total dose of 400 mg per week. Iron balance, as determined by TSAT and ferritin, was maintained in both groups throughout the study, with no significant difference in TSAT (Fig. 2A) or ferritin (Fig. 2B) between the two groups (Table 2). Reticulocyte hemoglobin, a marker of iron deficiency, was 28.4 ± 2.9 pg in the dialysate iron group versus 27.0 ± 3.5 pg in the i.v. iron group at month 2 ($P = 0.32$) and did not change significantly between the two groups during the course of the treatment phase of the study (Table 2). The TIBC was significantly higher in the dialysate iron group compared with the i.v. iron group in month 6 ($P < 0.05$), despite no significant differences in iron parameters or the nutritional status of the two groups.

During month 0, the weekly dose of i.v. iron dextran in the dialysate iron group was 69 ± 28 mg compared with

Table 2. Summary of efficacy parameters: A comparison of month 6 with pre-treatment (month 0)

Parameter	Pre-treatment		Month 6	
	Dialysate iron	i.v. iron	Dialysate iron	i.v. iron
Hemoglobin *g/dl*	10.6 ± 0.8	10.1 ± 1.1	10.1 ± 1.1	10.1 ± 1.4
Hematocrit %	33.4 ± 2.4	32.6 ± 3.7	32.0 ± 3.9	33.0 ± 4.2
Retic. hemoglobin *pg*	not done	not done	28.8 ± 2.0	28.3 ± 3.0
Serum iron *μg/dl*	54 ± 20	53 ± 22	54 ± 14	50 ± 20
TIBC *μg/dl*	222 ± 44	193 ± 48	235 ± 57[a]	180 ± 42
TSAT %	25 ± 7	27 ± 9	24 ± 7	26 ± 5
Ferritin *μg/liter*	210 ± 89	213 ± 53	155 ± 121	261 ± 212
Erythropoietin dose *units/dialysis session*	3990 ± 2370	5647 ± 2519	4418 ± 2299	5392 ± 2640
i.v. iron dextran dose *mg/week*	69 ± 28	60 ± 47	10 ± 23[ab]	56 ± 37

Plus-minus values are mean ± SD. Abbreviations are: Retic. hemoglobin, reticulocyte hemoglobin; TIBC, total iron binding capacity; TSAT, transferrin saturation.
[a] $P < 0.05$ when compared to i.v. iron group at month 6
[b] $P < 0.05$ when compared to pre-treatment (month 0)

Table 3. Summary of safety parameters: A comparison of month 6 to pre-treatment

Parameter	Pre-treatment		Month 6	
	Dialysate iron	i.v. iron	Dialysate iron	i.v. iron
Albumin *g/dl*	3.8 ± 0.4	3.8 ± 0.4	3.8 ± 0.3	3.7 ± 0.5
Cholesterol *mg/dl*	161 ± 20	153 ± 33	160 ± 25	136 ± 26[a]
Triglycerides *mg/dl*	209 ± 140	127 ± 51	166 ± 79	131 ± 49
Dry weight *kg*	83.0 ± 17.4	73.3 ± 27.3	78.4 ± 19.5	69.5 ± 22.6
Serum calcium *mg/dl*	9.5 ± 0.9	9.4 ± 1.0	9.1 ± 0.7	8.9 ± 0.7
Serum phosphorus *mg/dl*	5.5 ± 1.5	5.4 ± 1.4	5.4 ± 0.4	5.3 ± 1.9
Episodes of hypotension during hemodialysis sessions	1.4 ± 1.9	1.7 ± 1.9	2.3 ± 2.7	3.0 ± 2.5

Plus-minus values are mean ± SD.
[a] $P < 0.05$ when compared to i.v. iron group pretreatment

60 ± 47 mg in the control group. Despite no significant differences in hemoglobin, TSAT, ferritin, and erythropoietin dose between the two groups, the requirements for i.v. iron dextran were significantly reduced during the treatment phase in the dialysate iron group (Fig. 1C).

The decrease in i.v. iron requirements in the dialysate iron group was accompanied by a concentration-dependent transfer of iron from dialysate to the blood compartment, as demonstrated by an increase in postdialysis TSAT from 31.7 ± 6.8% on 2 μg/dl to 54.7 ± 9.9% on 8 μg/dl and 71.8 ± 13.4% on 12 μg/dl iron concentration (Fig. 3A). The increment in TSAT postdialysis remained constant when dialysate iron concentration was maintained at 12 μg/dl for three months. Although we had not planned to routinely monitor the decline in serum iron parameters following dialysis, in one of these patients, a rapid decline in the TSAT and serum iron concentration occurred over one hour, following the end of a hemodialysis session (Fig. 3B).

Safety parameters

There was no evidence of pulmonary or tracheobronchial toxicity by history or physical examination at the end of the study. Hypersensitivity reactions were not encountered in either group. Overt anemia requiring blood transfusions developed because of excessive gastrointestinal blood loss in one of the i.v. iron group patients. Two patients in the dialysate iron group required blood transfusions, one following coronary artery bypass surgery and the other following the amputation of a lower extremity. None of the patients exhibited evidence of iron overload on clinical or laboratory testing. Postdialysis TSAT was monitored considering the potential toxicity of free plasma iron if the binding capacity of transferrin was exceeded. In 6 of the 10 patients in the dialysate iron group, there were 12 instances when the postdialysis TSAT exceeded 90%, with no associated signs or symptoms of iron toxicity. On three occasions in three different patients, the TSAT immediately postdialysis ranged from 100 to 109%. None of these patients exhibited any signs or symptoms of iron toxicity during these occurrences. The nutritional parameters were unchanged for the duration of the study. Serum calcium and phosphorus were not significantly altered when comparing month 0 to month 6. Predialysis and postdialysis blood pressures were not significantly different between the two groups at any time during the study (data not shown). Hypotension, as defined by systolic blood pressure of less than 100 mm Hg or diastolic blood pressure less than 60 mm Hg, occurred with equal frequency in the two groups (Table 3).

Febrile reactions during hemodialysis secondary to ex-

cessive bacterial content of the dialysate were not observed in either group, and there was no evidence for bacterial overgrowth in iron-containing bicarbonate concentrates. Iron-containing dialysis solutions did not have any adverse effect on dialyzer reuse or hemodialysis equipment, including the sensors and dialysis tubing.

DISCUSSION

Soluble iron salts have hitherto been considered too toxic for parenteral administration because the free iron catalyzes formation of oxygen free radicals. We have demonstrated that soluble ferric pyrophosphate can be infused directly into the circulation by dialysis without any apparent toxicity. No short-term adverse effects were noted, even on occasions when the postdialysis TSAT ranged between 90 and 108% while patients were dialyzed against a dialysate iron concentration of 12 μg/dl. This may be related to the high affinity of iron for pyrophosphate that is of the same order of magnitude as the affinity of iron for transferrin. Therefore, ferric pyrophosphate is a stable molecule that does not ionize readily (pK_A 22.2), resulting in negligible release of free iron, even when the binding capacity of transferrin is exceeded. Studies with another metal pyrophosphate complex, stannous pyrophosphate, have reported immediate toxic effects, presumably from binding of pyrophosphate moiety to calcium in the blood [24]. Hypocalcemia was not observed in patients receiving ferric pyrophosphate, as the ferric ion is more strongly complexed by pyrophosphate than is the stannous ion (pK_i approximately 5) or the calcium ion (pK_i approximately 5 to 8) [25, 26].

The colloidal iron compounds are processed in the reticuloendothelial system before iron is released into the circulation. On the other hand, pyrophosphate moiety in circulating ferric pyrophosphate is directly able to trigger iron transfer to transferrin, between transferrin molecules and between transferrin and ferritin [16–19] without the need for prior processing by the reticuloendothelial system. In this respect, metabolism of ferric pyrophosphate resembles physiological processing of iron delivered into the circulation after absorption by the gut. The differences in metabolism of soluble and colloidal iron compounds may be responsible for the divergent trends in serum ferritin concentration during the course of the study (Fig. 2B). With the maximum dialysate concentration of ferric pyrophosphate tested, the TSAT increased from a predialysis level of 23.6 ± 7.1% to 74.2 ± 17.2% at the end of hemodialysis and returned to the predialysis levels within 48 hours. This decline in TSAT following infusion of ferric pyrophosphate is much more rapid compared with when 50 or 100 mg of i.v. iron dextran is administered (A. Besarab, unpublished data). The mean weekly i.v. iron require-

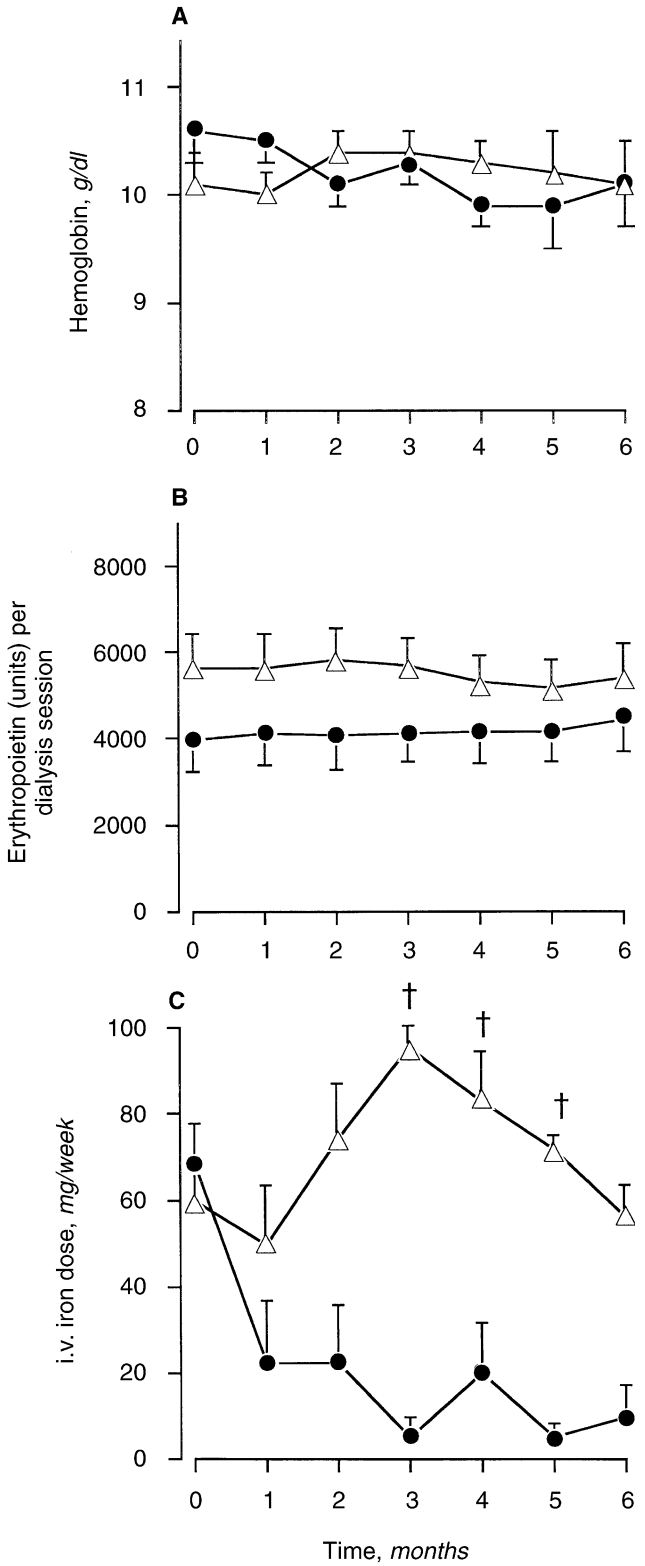

Fig. 1. Whole blood hemoglobin (*A*) and erythropoietin dose per hemodialysis session (*B*) three times a week remained stable during the course of the study (mean ± SE). Symbols are: (●) dialysate iron group; (△) i.v. iron group. The average weekly intravenous iron dose (*C*) was similar in the two groups during the pretreatment phase (month 0). During the treatment phase (month 1 to 6), patients receiving dialysate iron had a significantly decreased requirement for i.v. iron compared with the group receiving i.v. iron alone. $*P < 0.05$, $†P < 0.003$, dialysate iron group vs. i.v. iron group; $‡P < 0.003$, pretreatment vs. month 6 within the dialysate iron group.

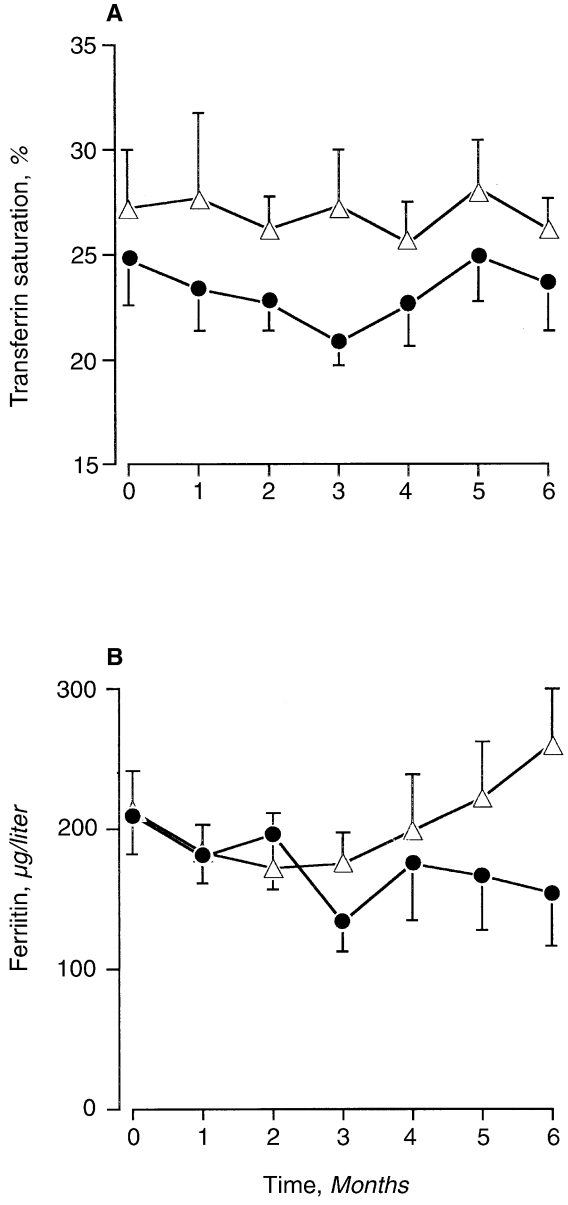

Fig. 2. Predialysis serum transferrin saturation (*A*) and serum ferritin (*B*). There was no significant difference between the two groups. Also, there was no significant change from baseline over time within each group. Data are means ± SE. Symbols are: (●) dialysate iron group; (△) i.v. iron group.

ment was reduced by approximately 40 mg in the dialysate iron group, suggesting that approximately 10 to 15 mg of iron are delivered via the dialysate during each hemodialysis.

It is estimated that nearly two thirds of the maintenance hemodialysis population in the United States is receiving i.v. iron dextran (Amgen Inc., Thousand Oaks, CA, USA), the only iron compound available for parenteral administration in the United States at this time. Furthermore, the use of i.v. iron is expected to increase following the recommendations by the National Kidney

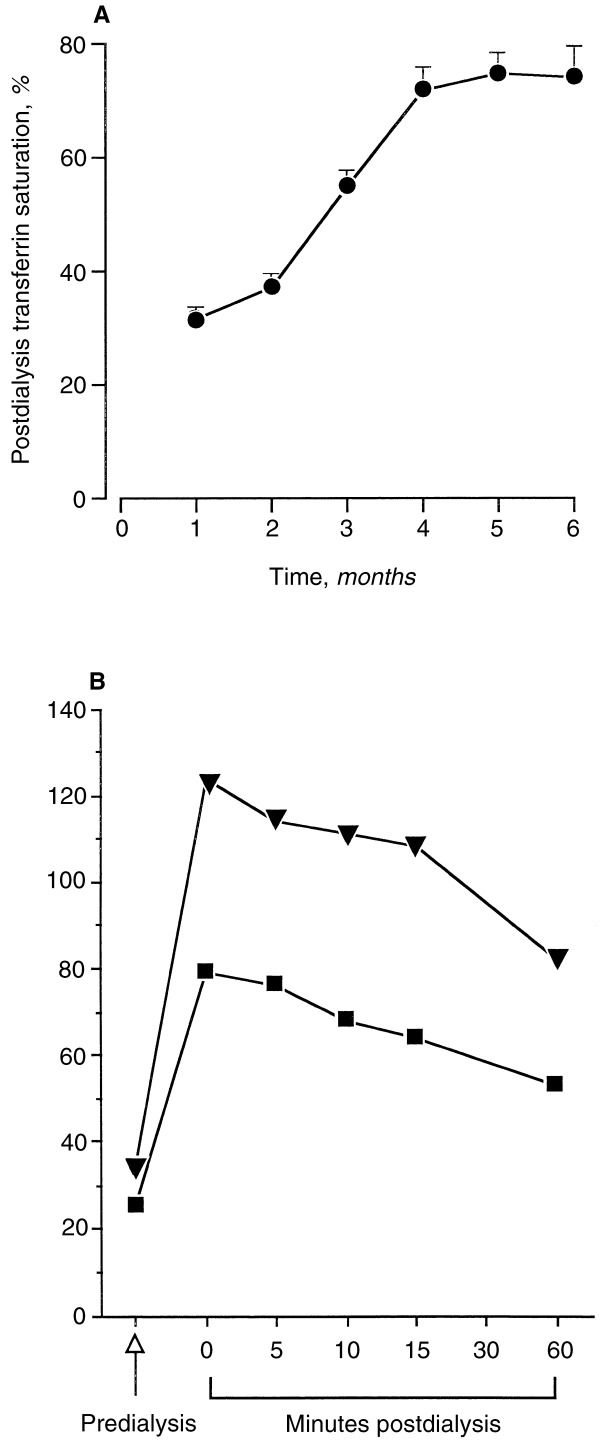

Fig. 3. Postdialysis serum transferrin saturation (TSAT) indicated a concentration-dependent increase as dialysate iron concentration was increased from 2 to 12 µg/dl, and TSAT remained stable during the last three months when the dialysate iron concentration was maintained at 12 µg/dl (*A*). In a patient, TSAT and serum iron were measured over one hour, following completion of a dialysis session using 12 µg/dl dialysate iron; a rapid decline in TSAT and serum iron was noted (*B*). Symbols are: (●) dialysate iron group; (▼) serum iron (µg/dl); (■) transferrin saturation (%).

Foundation-Dialysis Outcome Quality Initiative [20]. Intravenous iron dextran therapy is associated with arthralgia–myalgia syndrome in 4.7% and serious or life-threatening reactions in 0.7% of patients [27]. Because acute reactions can occur after subsequent dosing, a test dose is recommended before every course of parenteral iron therapy [27]. Furthermore, iron dextran induced loin and epigastric pain, or hypotension may interfere with the dialysis treatment. There is also concern about potential iron overload with i.v. therapy, leading to increased risk of infection and possibly cancer [28]. Furthermore, frequent administration of i.v. iron dextran to maintenance hemodialysis patients may be associated with increased risk of mortality from all causes and specifically from infections and cardiac diseases (i.v. iron dosing patterns and mortality; abstract; Collins et al, *J Am Soc Nephrol* 9:205A, 1998).

This study demonstrated that transfer of soluble ferric pyrophosphate into the circulation by the process of hemodialysis is effective in maintaining iron balance. Although the actual amount of iron transferred by hemodialysis was not measured, it was sufficient to maintain an iron balance in 8 of the 10 patients, without an additional need for oral or i.v. iron supplementation. The two patients who required additional iron had an interruption in their dialysate iron therapy because of hospitalization and suffered excessive iron losses consequent to surgery. This suggests that dialysate iron therapy may be able to maintain iron balance in the majority of hemodialysis patients and thereby forego any adjunctive oral or i.v. iron supplementation. However, in some patients, particularly when there is excessive blood loss, additional oral or i.v. iron supplements may be required. Dialysate iron use is likely to significantly decrease the need for i.v. iron in maintenance hemodialysis patients. In addition to the indirect cost associated with morbidity and hospitalizations, the direct cost of i.v. iron administration adds significantly to the hemodialysis cost. A recent pharmacoeconomic analysis of anemia management in maintenance hemodialysis patients showed that optimal treatment with i.v. iron can reduce the dose of erythropoietin by 35%, but the estimated cost savings were largely offset by the cost of i.v. iron [29]. The cost of ferric pyrophosphate is only a small fraction of the cost of iron dextran. Intravenous iron supplementation is often required for the treatment of iron deficiency in chronic peritoneal dialysis patients receiving erythropoietin [30]. Preliminary studies have shown that serum iron levels could be normalized in iron-deficient rabbits when acute peritoneal dialysis was performed using ferric pyrophosphate fortified dialysis solution (A. Gupta, unpublished data). Therefore, dialysate iron therapy also holds promise for peritoneal dialysis patients.

In the general population, oral iron supplementation programs have failed because of noncompliance [9]. The side-effects and expense associated with i.v. or intramuscular colloidal iron compounds have limited their application. The safety and efficacy of slow ferric pyrophosphate infusion by hemodialysis suggest feasibility of parenteral administration of this compound to nondialysis patients, although this merits further investigation. Water solubility and the relatively small molecular weight of ferric pyrophosphate, compared with colloidal iron compounds, suggest that it may be suitable for use in transdermal or subcutaneous delivery systems. The feasibility of administering ferric pyrophosphate to nondialysis patients by the parenteral route needs to be determined by further elucidation of its ferrokinetics and metabolism, including transfer of iron to transferrin, assessment of direct uptake by the tissues, and safety when the iron-binding capacity of transferrin is exceeded.

In conclusion, we have demonstrated that iron can be infused into the circulation by the process of dialysis when ferric pyrophosphate is added to the hemodialysis solution. A dialysate iron concentration of 12 μg/dl was found to be safe, and the amount of iron transferred was sufficient to maintain iron balance in a majority of maintenance hemodialysis patients, thereby significantly reducing the requirements for i.v. iron supplementation. This novel method of iron administration to hemodialysis patients merits further investigation to determine its long-term safety and efficacy.

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