Pediatr Nephrol (2001) 16:779–783

DIALYSIS / ORIGINAL ARTICLE

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Maintenance intravenous iron therapy in pediatric hemodialysis patients

Received: 13 November 2000 / Revised: 23 April 2001 / Accepted: 24 April 2001

Abstract Iron supplementation is required for optimal response to erythropoietin (EPO) in hemodialysis patients. This is due to blood lost in the dialysis tubing after dialysis and the increased demand for iron by EPO therapy. Maintenance intravenous (IV) iron was administered according to a standardized protocol to pediatric patients on hemodialysis in our institution. The effect of this protocol on EPO dose, iron indices, anemia, and medication costs was evaluated. Data on two groups of patients were retrieved from the health records. Group 1 (n=14) consisted of patients treated in the 18 months prior to the protocol. These patients received oral iron supplements and occasional IV iron. Group 2 (n=5) consisted of all patients treated with the IV iron protocol. There was no difference in clinical characteristics and mean values for monthly hemoglobin, serum iron, ferritin, and transferrin saturation between groups. The dose of EPO was significantly reduced in group 2 compared with group 1 (193.9±121.4 vs. 73.9±39.0 units/kg per week, P<0.05). Medication costs were reduced by 26% in group 2. No significant adverse events were seen. Maintenance IV iron reduced the dose of EPO required to maintain blood hemoglobin levels. Our results also suggest that maintenance IV iron is a more-economic method of iron supplementation for pediatric hemodialysis patients.

Keywords Hemodialysis · Intravenous iron · Erythropoietin · Cost analysis

Introduction

Erythropoietin (EPO) is required for the optimal treatment of anemia in chronic renal failure. Iron deficiency is an important cause of an attenuated response to EPO therapy in hemodialysis patients. This results from the continued blood loss in the dialysis circuit and the increased demand for iron by EPO therapy. Oral iron supplements may be insufficient to maintain total body iron stores or iron available for erythropoiesis [1]. Maintenance intravenous (IV) iron supplementation has been shown, in adults on hemodialysis, to reduce the dose of EPO that is required to maintain hemoglobin levels [2]. Pediatric data are limited. Two studies have demonstrated the efficacy of standardized courses of IV iron dextran in anemic and iron-deficient pediatric hemodialysis patients [3, 4].

In our institution patients previously received oral iron supplements and IV iron on an individual, as required basis. Because of poor compliance with oral iron supplements and variable IV iron prescribing, a protocol was introduced to administer IV iron to all pediatric patients on chronic hemodialysis in place of oral iron supplements. In this way IV iron was used, not on the basis of iron deficiency or anemia, but as the patient's maintenance iron supplement. We compared the effect of this maintenance IV iron protocol on EPO dose, iron indices, anemia, and medication costs in those patients treated before (group 1) and after (group 2) the introduction of the protocol.

Materials and methods

Iron (III) hydroxide sucrose complex (Venofer) was used as the IV iron supplement. Oral iron supplements were discontinued and IV iron administered according to the protocol described in Table 1. EPO was prescribed independently of iron studies to maintain the blood hemoglobin in the range of 11–12 g/dl. The clinical practice was to adjust the dose by 25% to achieve this range.

All patients on chronic hemodialysis for more than 3 continuous months were available for inclusion. The patients were divided into two groups. Group 1 included all patients dialyzed in the 18 months prior to the introduction of the new protocol. These served as a historical control and represented the previous iron administration practice. Oral iron was prescribed up to a limit of 6 mg/kg per day as clinically indicated. This group included patients who had received occasional IV iron on an ad-hoc basis. Group 2 included all patients treated since the introduction of the maintenance IV iron protocol.

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Table 1 Protocol for maintenance intravenous iron in pediatric hemodialysis patients (*TSAT* transferrin saturation)

Drug	Vifor International	Venofer [iron (III) hydroxide complex]
Regimen	No. 1	Maintenance If TSAT >20% but <50% and ferritin >100 but <800 µg/l 2 mg/kg per dose given once weekly, maximum single dose 100 mg
	No. 2	Accelerated If TSAT <20% or ferritin <100 µg/l 7 mg/kg per dose×1 dose for 1st week, maximum single dose 200 mg Then 2 mg/kg per dose given once weekly, maximum single dose 100 mg
	No. 3	No treatment If TSAT >50% or ferritin >800 µg/l Regardless of treatment group or hemoglobin value, if TSAT >50% or ferritin >800 µg/l, intravenous iron therapy should be stopped and restarted only once the patient meets the criteria for treatment no. 1 or no. 2

Data on patients who required hospital admission or treatment for sepsis were not collected until 1 month after the event. Routinely collected monthly data on hematological indices (hemoglobin and reticulocyte count) and iron stores (serum iron, ferritin, transferrin, and calculated transferrin saturation [TSAT; iron/(2×transferrin)] were retrieved from the case record for patients in each group. Blood samples were drawn on the first Monday of each month; IV iron was administered on each Friday. An estimate of dialysis efficiency was determined by the monthly urea reduction ratio (URR). Parathyroid hormone and aluminum levels were recorded because of their effects on hematopoiesis [5, 6]. The patients' weights were determined by the mean post-dialysis weight for each month. Medication doses were determined from the prescription record and dialysis chart. Relative medication costs were calculated from prices provided by the hospital pharmacy. The total cost for each medication was determined for the duration of therapy. This was then divided to determine a mean cost per month for the whole treatment period and adjusted for body weight.

Data are presented as means with standard deviations and medians with ranges. Groups were compared using Student's *t*-test and Mann-Whitney rank sum test. $P<0.05$ was accepted as significant.

Results

Fourteen patients were included in group 1, with a median duration of data collection of 5.0 months (range 3.0–6.0 months). Five patients were included in group 2, with a median duration of data collection of 5.0 months (range 3.0–5.0 months). Three patients were treated with both iron administration strategies. The clinical characteristics are described in Table 2. There were no significant differences for any of the parameters. Data on the menstrual status of female patients were not available. All patients in group 1 had been on dialysis and EPO therapy for at least 1 month prior to the collection of data. One patient in group 2 started EPO and hemodialysis 2 weeks before data were collected. Blood transfusion requirements prior to EPO therapy were not available. No patients received aluminum-containing phosphate binders. There was no significant difference in the parameters that may affect the clinical response to EPO: dialysis dose (estimated by the URR), hyperparathyroidism, or blood aluminum level.

Table 2 Clinical characteristics. Group 1: oral and intermittent intravenous iron. Group 2: maintenance intravenous iron. (*PTH* parathyroid hormone, *URR* urea reduction ratio)[a]

	Group 1	Group 2	*P*
Number	14	5	
Sex (M:F)	7:7	4:1	
Age (years)	11.0±5.4	11.2±4 .4	0.90
Weight (kg)	36.8±20.8	40.7±16.6	0.71
Duration of hemodialysis (months)	8.7±8.2	5.1±4.4	0.36
Aluminum (mmol/l)[b]	292±189[a]	244±90	0.50
PTH (ng/l)	266±301	232±282	0.61
URR (%)	74±5	74±4	0.90

[a] Mean±SD
[b] Only 9 of 14 patients had aluminum levels measured

Table 3 Iron and hematological indices. Group 1: oral and intermittent intravenous iron. Group 2: maintenance intravenous iron[a]

Parameter	Group 1	Group 2	*P*
Hemoglobin (g/dl)	11.1±0.5	11.4±0.6	0.30
Reticulocytes ($\times 10^6$/l)	73.3±27.9	71.8±12.7	0.91
Iron (µmol/l)	10.4±3.5	12.4±4.5	0.33
Ferritin (µg/l)	232.6±217.1	375.3±238.6	0.18
Transferrin (µmol/l)	25.5±6.6	25.1±9.5	0.47
TSAT (%)	21.9±4.8	28.3±11.8	0.36

[a] Parameters are mean±SD

The mean prescribed dose of oral iron therapy in group 1 was 4.0±1.9 mg/kg per day. Eight patients in group 1 received ten courses (mean duration, 5.6±4.3 weeks) of intermittent IV iron therapy. The indication for IV treatment was assessed clinically and included evaluation of anemia, iron stores, and non-compliance with oral medication. The mean dose of IV iron in these 8 patients was 3.3±2.2 mg/kg per week (P=0.052 vs. group 2, 1.76±0.09 mg/kg per week). There was a greater range of prescribed doses in group 1 compared with group 2 (0.7–7.2 mg/kg per week vs. 1.7–1.9 mg/kg per week).

There was no difference in the hematological indices or iron stores between groups (Table 3). Two patients in

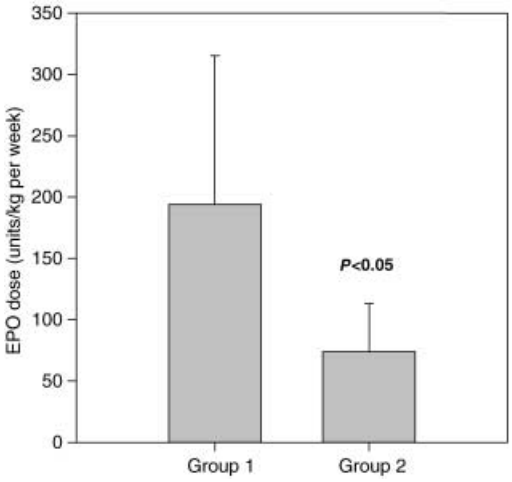

Fig. 1 Mean erythropoietin (*EPO*) dose. Group 1: oral and intermittent intravenous iron. Group 2: maintenance intravenous iron

group 1 had 1 month during which the serum ferritin was >800 ng/ml. This was at the time of intermittent IV iron administration in 1 patient. There were no patients in group 1 with a persistently elevated mean serum ferritin over the period of data collection. One patient in group 1 had TSAT >50%, not associated with intermittent IV iron.

There were no patients with serum ferritin >800 ng/ml at any time in group 2. One patient in group 2 had an elevated TSAT (>50%) for 3 months. He had nephrotic syndrome, due to focal segmental glomerulosclerosis, and low transferrin levels, mean 8.5 μmol/l. Two other patients in group 2 had 1 month in which the TSAT exceeded 50%. These occurred after 12 weeks of IV iron at a dose of 1.7 mg/kg per week and 8 weeks of 1.8 mg/kg per week. Two patients in group 2 received a dose of 200 mg IV iron (regimen no. 2) on one occasion each. No adverse effects were seen in either treatment group. A test dose was given to all patients in group 2, consisting of 25% of the treatment dose infused over 15 min.

All patients received IV EPO. There was a significant reduction in the mean dose of EPO given to those patients in group 2 compared with group 1 (mean EPO dose 193.9±121.4 vs. 73.9±39.0 units/kg per week, $P<0.05$). (Fig. 1.)

All costs were calculated in Canadian dollars. Group 2 was associated with a 26% reduction in the cost of EPO and iron combined compared with group 1 (median cost 7.8, range 5.3–11.8 $/kg per month vs. 9.3, range 5.5–32.5 $/kg per month, $P=0.33$). EPO therapy accounted for 84% of the mean total drug cost in group 1 and 48% in group 2. Group 2 was associated with a reduced mean cost of EPO therapy of 66%, while the mean cost of iron therapy increased by 48%, thus leading to an overall reduction in cost.

Discussion

The use of EPO has revolutionized the treatment of renal failure. The improvement in blood hemoglobin level leads to an increase in physical and mental performance and overall well-being [7, 8]. For optimal hemopoietic response to EPO, hemodialysis patients require iron supplementation to maintain adequate iron stores [9]. There is a large body of evidence supporting the use of IV iron in adult hemodialysis patients [2, 9, 10, 11, 12]. The current trend in adult studies has been towards regular IV iron (maintenance therapy) in place of oral iron supplements [10, 11, 13]. Oral iron supplements have many well-recognized drawbacks [4].

We report the use of a standardized IV iron protocol in pediatric hemodialysis patients, in which IV iron was used as maintenance therapy in place of oral iron supplements. Like others, we have demonstrated that IV iron improves the efficiency of EPO [3, 4]. Unlike previous reports, we have reported the use of IV iron in patients who were not selected on the basis of anemia or iron deficiency. We provide a comparison with our previous iron management that suggests maintenance IV iron is more effective than intermittent dosing in pediatric patients.

The most-appropriate dosage regimen for IV iron in pediatric patients has yet to be determined. Many adult studies have used standardized doses unrelated to body weight [10, 12, 13, 14]. This is inappropriate for pediatric dosing [15]. The rationale for the maintenance IV iron protocol was to replace iron lost in the dialysis circuit. However there are no data on the iron need of pediatric patients on hemodialysis. Pediatric IV iron doses have ranged from 1 to 4 mg/kg per week for up to 12 weeks [3, 4, 7]. We adopted a conservative approach, treating patients with 2 mg/kg per week and loading those thought to have iron deficiency with a single dose of 7 mg/kg followed by 2 mg/kg per week.

The reduction in EPO dose by maintenance IV iron may have beneficial safety and economic effects. Hypertension is the most-common side effect of EPO therapy and occasionally requires dose reduction [7]. EPO has several effects on endothelial and vascular smooth muscle biology that contribute to hypertension [16]. Improvements in EPO-related hypertension can be achieved by changing the route of administration from IV to subcutaneous, with an associated dose reduction [17, 18]. Our current practice is to administer IV EPO to pediatric hemodialysis patients. Maintenance IV iron enables a dose of EPO similar to that used when EPO is administered subcutaneously [17, 18]. Data on blood pressure were not collected for our patients.

Our results suggest that pediatric hemodialysis patients can be more economically managed with the use of maintenance IV iron. Similar economic benefit has been demonstrated in adult patients [12, 19, 20]. Although not statistically significant, the 26% cost reduction reported here represents a clinically and financially significant improvement in health care costs. This cost reduction was seen despite accounting for the cost of discarded medication, as Venofer is available only as single-use ampoules containing 200 mg. Targeting a higher level of TSAT (30%–50%) and further EPO reduction may further increase cost savings [13].

There is concern over the reliability of routinely measured iron stores when samples are taken close in time to infusions of IV iron [1, 9]. We were influenced by the data of Besarab et al. [14] indicating that iron stores could be monitored accurately during weekly IV iron therapy. A once-weekly dose schedule was used to avoid oversaturation of transferrin, attempting to reduce the effects of excessive unbound iron in the circulation. The limitations of ferritin and TSAT for determining iron overload are well recognized. Serum ferritin concentrations alone can lead to inaccurate assessment of body iron load [21, 22]. Hepatic iron concentration does not correlate significantly with serum transferrin or ferritin levels after multiple blood transfusions [23]. Despite this, the target ranges of 100%–800 ng/ml for ferritin and 20%–50% for TSAT were chosen based on published guidelines [1]. Although there is some evidence that targeting higher levels may further improve the efficacy of EPO [13], it was not our purpose to investigate these limits.

Alternative techniques (e.g., reticulocyte hemoglobin concentration and red blood cell ferritin) for monitoring iron status may improve efficacy of any iron treatment regimen by providing alternate thresholds for the initiation and termination of IV iron [24, 25]. Unfortunately these are not widely available. We used standard measures of iron stores, imposing the least-possible change to overall dialysis management. This enabled the protocol to be designed with weekly dosing and without interruption to our standard practice of measuring the iron stores once monthly.

Iron (III) hydroxide sucrose complex is associated with a very good safety profile [26]. After initial anxiety in our institution regarding the use of maintenance IV iron, this regimen was found to be straightforward to follow and with no adverse events in the patients treated to date. Our study was too small to quantify a difference in adverse events.

The risk of iron overload with long-term IV iron therapy is difficult to determine [9]. For pediatric patients, there is little information in the literature that clearly establishes the safe upper limit for ferritin and TSAT. Adult patients are potentially at more risk with respect to cardiovascular disease [27]. This makes direct comparison with adult-based data difficult. Only group 1 was associated with elevated ferritin levels. It was reassuring that no patients within group 2 had elevated ferritin levels, although this group was more frequently associated with an elevated TSAT. The true significance of these findings remains unclear. Transfusion-dependent hematological conditions develop significant iron overload only after some years [28]. This may be related to genetic factors, such as the hemochromatosis allele [29]. Currently in our center the duration of hemodialysis prior to renal transplantation is approximately 12 months. We believe that with closely monitored iron indices these patients are unlikely to develop significant iron overload.

In conclusion, we have demonstrated that a standardized maintenance IV iron protocol is valuable when managing anemia in pediatric hemodialysis patients. Despite the small sample size we have determined that it is more efficacious than our previous practice of intermittent IV iron therapy. Maintenance IV iron therapy allows the blood hemoglobin level to be maintained with a lower dose of EPO. There is cost saving to be gained by the use of maintenance IV iron. The increase in iron cost is more than offset by the reduction in EPO cost. We have not experienced any significant adverse effects to date. The optimum dose of IV iron required in pediatric patients to improve erythropoiesis without causing iron overload has yet to be determined.

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LITERATURE ABSTRACTS

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Olive oil and reduced need for antihypertensive medications

Arch Intern Med (2000) 160:837–842

Background The blood pressure (BP) effects of changing the total fat intake and saturated-unsaturated fat ratio are still controversial, despite evidence that saturated fat-enriched diets are associated with higher BP levels. This double-blind, randomized crossover study evaluated a possible difference between antihypertensive effects of monounsaturated (MUFA) (extra-virgin olive oil) and polyunsaturated fatty acids (PUFA) (sunflower oil).
Methods Twenty-three hypertensive patients were assigned randomly to MUFA or PUFA diet for 6 months and then crossed over to the other diet; effects were evaluated on the basis of daily antihypertensives needed.
Results Diets high in MUFA and PUFA differed from the habitual diet for reduced total and saturated fats, whereas they differed from each other for MUFA (17.2% vs 10.5%) and PUFA content (3.8% vs 10.5%). Resting BP was significantly lower (P=0.05 for systolic BP; P=0.01 for diastolic BP) at the end of the MUFA diet compared with the PUFA diet. Blood pressure responses during sympathetic stimulation with the cold pressor test and isometric exercise were similar. Daily drug dosage was significantly reduced during the MUFA but not the PUFA diet (–48% vs –4%, P<0.005). All patients receiving the PUFA diet required antihypertensive treatment, whereas 8 of those receiving the MUFA diet needed no drug therapy.
Conclusions A slight reduction in saturated fat intake, along with the use of extra-virgin olive oil, markedly lowers daily antihypertensive dosage requirement, possibly through enhanced nitric oxide levels stimulated by polyphenols.

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Potassium-magnesium citrate versus potassium chloride in thiazide-induced hypokalemia

Kidney Int (2000) 57:607–612

Background The purpose of this study was to compare the value of potassium-magnesium citrate (KMgCit) with potassium chloride in overcoming thiazide-induced hypokalemia.
Methods Sixty normal subjects first took hydrochlorothiazide (HCTZ; 50 mg/day). After three weeks of treatment (or earlier if hypokalemia developed), they were randomized to take KMgCit (42 mEq K, 21 mEq Mg, and 63 mEq citrate/day) or potassium chloride (42 mEq/day) for three weeks while continuing on HCTZ.
Results KMgCit significantly increased the serum potassium concentration from 3.42±0.30 mEq/L on HCTZ alone to about 3.8 mEq/L (P<0.001). Potassium chloride produced a similar increase in serum potassium concentration from 3.45±0.44 mEq/L to about 3.8 mEq/L (P<0.001). KMgCit significantly increased the serum magnesium concentration by 0.11 to 0.12 mEq/L (P<0.01), whereas potassium chloride produced a marginal decline or no significant change. KMgCit was less effective than potassium chloride in correcting HCTZ-induced hypochloridemia and hyperbicarbonatemia. KMgCit, but not potassium chloride, significantly increased urinary pH (by about 0.6 unit), citrate (by about 260 mg/day), and urinary magnesium.
Conclusions KMgCit is equally effective as potassium chloride in correcting thiazide-induced hypokalemia. In addition, KMgCit, but not potassium chloride, produces a small but significant increase in serum magnesium concentration by delivering a magnesium load, and it confers alkalinizing and citraturic actions.