Intravenous Iron Administration during the Maintenance Period in Erythropoietin-treated Hemodialysis Patients: A Simple and Effective Method

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Objectives: *To determine the interval of intravenous iron administration during maintenance iron therapy in erythropoietin-treated hemodialysis patients.*
Material and Method: *The method of maintenance intravenous iron therapy has been studied in 20 stable erythropoietin-treated hemodialysis patients who have iron deficiency anemia diagnosed by transferin saturation (TSAT) below 20%.*
Results: *After receiving 1,000 mg of intravenous iron as the first loading dose, the TSAT was increased from 16.4 ± 0.5 to 29.3 ± 2.6% ($p < 0.05$). After 155.6 ± 7.3 days, such values was reduced to 16.3 ± 1.4% ($p < 0.05$). The second loading dose was administered and could raise the TSAT to 33.7 ± 3.9% ($p < 0.05$). The patients, then, received 100 mg of intravenous iron for every 15.6 ± 2.9 days, one-tenth of the duration between the two loading doses. The values of TSAT at 1,2,3,4,5 and 6 months after the second loading dose were 38.5 ± 2.4, 37.1 ± 0.2, 34.2 ± 3.6, 34.1 ± 3.3, 35.3 ± 4.1, and 36.5 ± 3.1% (NS).*
Conclusion: *As such, in erythropoietin-treated hemodialysis patients, after loading with 1,000 mg, prescription of 100 mg of intravenous iron for every 2 weeks could maintain the TSAT levels above 20%.*

Keywords: *Hemodialysis, Iron deficiency anemia, Intravenous iron therapy, TSAT*

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The most common cause of a less response to erythropoietin in hemodialysis patients is iron deficiency anemia, defined by transferin saturation (TSAT) below 20% or serum ferritin of lower than 100 ng/mL [1-3]. The values of TSAT are preferably used in clinical practice since serum ferritin levels can vary with various factors [4]. The 1997 ESRD (end stage renal disease) core had demonstrated that the incidence of iron deficiency anemia was 30% in 7,292 hemodialysis patients [5].

In 1997 as well as in 2000, the Anemia Work Group of National Kidney Foundation-Dialysis Outcome has recommended that hemodialysis patients should be treated with a loading dosage of 1,000 mg of intravenous iron, 100 mg for 10 consecutive hemodialysis sessions [5,6]. To maintain the TSAT level above 20%, this is followed by a maintenance dose of 25-100 mg/week of intravenous iron [5,6]. This is on opinion basis of the specialist. Heretofore, there is no evidence-based method of how to appropriately prescribe the maintenance iron therapy regarding the dose and the interval of intravenous iron administration.

The present work was performed to verify a new method in prescribing a more accurate maintenance dosage for the hemodialysis patients to stabize the TSAT level above 20%.

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Material and Method

Patients

The study was performed in 20 ESRD patients, 10 men and 10 women, who received twice-a-week hemodialysis treatment, 4 hours for each hemodialysis session, at King Chulalongkorn Memorial

Hospital, Bangkok Thailand. The study was approved by the Ethical Committee, Faculty of Medicine, Chulalongkorn University. Informed consent was obtained from each patient. The patients had been dialyzed, twice a week, for at least 3 months and had stable hematocrit levels of more than 30 percent. All participating patients had to meet the following inclusion criteria: 1) duration of erythropoietin therapy > 3 months 2) transferrin saturation (TSAT) ≥ 20% and serum ferritin ≥ 100 ng/mL 3) normalized protein catabolic rate (nPCR) ≥ 0.8 gm/kg ideal body weight per day 4) serum intact parathyroid hormone (iPTH) < 1,000 pg/mL, and 5) the values of Kt/V, which was used to determine the adequacy of hemodialysis and was calculated by rate adjustment of single pool-variable formula by Daugirdas, ≥ 3.6 per week [7]. The exclusion criteria were: 1) obvious bleeding or positive for stool occult blood in the past 2 months, 2) receiving blood transfusion in the past 3 months, 3) anaphylaxis to intravenous iron, 4) hospitalization in the past 4 weeks, 5) operation in the past 3 months, 6) malignancy, 7) the serum ferritin levels > 1,000 ng/mL, 8) serum aluminum levels > 2.0 microgram/mL, and 9) HbsAg or Anti HCV or Anti HIV was positive.

Method

Pre-study period (Fig. 1)

In all studied patients, oral forms of iron were discontinued while folic acid at a dose of 5 mg/day was still prescribed.

Complete blood count (CBC) and the values of TSAT and ferritin levels were tested every 4 weeks. Without iron replacement, the patients would have gradually decreased TSAT levels until the values of TSAT were lower than 20% and, then, were enrolled in the study.

The first iron loading dosage period (TSAT < 20%) (Fig. 1)

Intravenous iron hydroxysaccharate (Venofer Natural Media, Thailand), 100 mg per vial, was utilized in the present study. Each patient was received intravenous iron at the dose of 100 mg during the last hour of each hemodialysis procedure for 10 consecutive hemodialysis sessions. The total loading dose of intravenous iron in each patient was 1,000 mg.

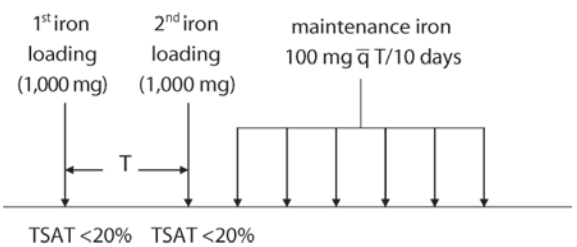

Fig. 1 Schematic experimental plan

Again, without oral iron supplement, CBC, TSAT, and ferritin concentrations were followed at every 4 weeks until the TSAT levels were less than 20%.

The second iron loading dosage period (TSAT < 20%) (Fig. 1)

Intravenous iron at the total dose of 1,000 mg, was given to the patients in the same method as the first loading dosage period.

The maintenance dosage period (Fig. 1)

After the second loading dosage of intravenous iron, 100 mg of intravenous iron had been prescribed to the patients for every one tenth of the time interval, T/10 days, between the two loading dosages (Figure 1). As in other periods, CBC, TSAT, and ferritin levels were followed at every 4 weeks.

Statistical Analysis

The TSAT levels at the time of 1, 2, 3, 4, 5, and 6 months after the second loading dosage were compared by the method of repeated measurement ANOVA. All data in the table and figures were expressed as mean ± S.E. and $P<0.05$ was considered to be statistically significant.

Results

Pre-study period

The mean values of the baseline characteristics of the 20 participating patients who completed the study were as followings : age = 54.0 ± 4.6 years, hematocrit = 35.4 ± 1.1%, TSAT = 35.9 ± 4.2%, serum ferritin = 599.0 ± 30.2 ng/mL, normalized protein catabolic rate = 1.1 ± 0.1 gm/kg/d, Kt/V = 2.2 ± 0.1 per hemodialysis session (4.4 ± 0.2 per week), intact parathyroid hormone = 299.8 ± 11.7 pg/mL, serum albumin = 4.1 ± 0.2 g/dL, and serum aluminum = 1.6 ± 0.1 mg/dL.

Without iron replacement therapy, the patients' mean TSAT values, at the time initially enrolled to the study, of 35.9 ± 2.1% were gradually reduced, for a duration of 132.6 ± 24.7 days, to the levels of 16.4 ± 0.5% ($P<0.01$) (Figure 2). The hematocrit levels were slightly decreased but the statistical significance was not attained (data not shown).

The first iron loading dosage period

Following the first iron loading dosage of 1,000 mg, the TSAT concentrations were increased to

29.3 ± 2.6% (P<0.05 vs the values before the first loading dose). Without iron supplement, following an averaged duration of 155.6 ± 7.3 days, the values of TSAT were again decreased to 16.3 ± 1.4% (P<0.05 vs the values after the first loading dose) (Fig. 2).

The second iron loading dosage period and the maintenance dosage period

The second iron loading dosage could increase the TSAT levels to 33.7 ± 3.9% (P<0.05 vs before the second loading dose) (Fig. 2). The maintenance dose of intravenous iron at the dose of 100 mg, given at a mean interval of 15.6 ± 2.9 days, 155.6 ± 7.3 divided by 10, could maintain the TSAT concentrations of 38.5 ± 2.4, 37.1 ± 0.2, 34.2 ± 3.6, 34.1 ± 3.3, 35.3 ± 4.1, and 36.5 ± 3.1% at 1, 2, 3, 4, 5, and 6 months, respectively (NS), after the second iron loading dose (Fig. 2).

In every studied period, the values of serum ferritin in all participating patients were less than 800 ng/mL (data not shown).

When compared with the baseline values, there were no significant alterations in hematocrit levels at any time points following the first iron loading dose until the end of the study. Also, when compared with the baseline values, no significant changes in other parameters mentioned above were noted throughout the study.

Discussion

Treatment of iron deficiency anemia in hemodialysis patients by intravenous iron has increased hemopoietic response to erythropoietin [8-10] and could reduce the amount of erythropoietin needed to achieve and maintain a target hematocrit / hemoglobin [11-13]. As such, intravenous iron administration in erythropoietin-treated hemodialysis patients is cost-effective [14] and has been increasingly utilized [5,6].

The recommendation of NKF-DOQI is to treat iron deficiency anemia in hemodialysis patients, whose TSAT values below 20% or/and serum ferritin levels below 100 ng/mL, by intravenous iron 100 mg given in 10 consecutive hemodialysis sessions. This is followed by a suggested maintenance dose of intravenous iron, ranging 25-100 mg/week, the dosage of which varied according to each patient [5,6]. Because of varying amount of blood loss in each hemodialysis session, in general practice, renal physicians give an initially estimated maintenance dose of intravenous iron to the patient, and then, adjust the dose through a period of

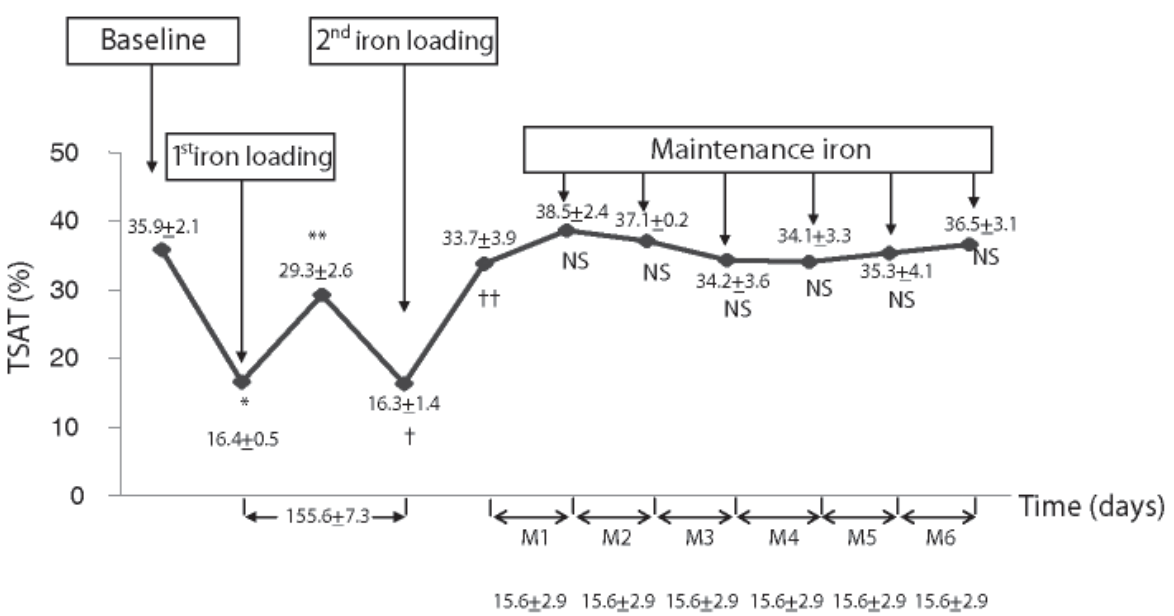

Fig. 2 TSAT values in different experimental periods
Abbreviation : M_1, M_2, M_3, M_4, M_5, and M_6 = maintenance period 1, 2, 3, 4, 5, and 6, respectively
* P<0.01 vs. baseline (35.9 ± 2.1%); ** P<0.05 vs. before 1st iron loading (16.4 ± 0.5%); † P<0.05 vs. the values after the 1st iron loading (29.3 ± 2.6%); †† P<0.05 vs. the values before the 2nd iron loading (16.4 ± 0.5%); NS = non significant when compared with the value at starting the maintenance iron (33.7 ± 3.9%)

time. In several patients, it is time consuming and, sometimes, is difficult to determine the appropriate interval in administering intravenous iron during maintenance period to stabilize the TSAT level above 20%.

The duration between the two maintenance doses and the dosage of each maintenance dose are the two factors involving in prescription of intravenous iron therapy during maintenance phase. Since the package of the commercially available intravenous iron is 100 mg per vial, the duration between the two maintenance doses is the sole factor to be determined. The present study was conducted to develop a simple method to identify the initially appropriate duration between the two maintenance doses. Indeed, intravenous iron at the loading dose of 1,000 mg can maintain the TSAT level over 20% for T days, the duration between the 2 loading doses. As such, 100 mg of intravenous iron would maintain the adequate TSAT levels for T/10 days (Fig. 1).

The present work has demonstrated that the method in calculating the duration between the two maintenance doses is simple and effective. The value of the duration can be used in clinical practice for maintaining the TSAT level higher than 20% for at least 6 months of the study (Fig. 2). Although the value of TSAT was assessed every 4 weeks in the current study, in general practice, the test can be determined in a longer interval, for examples : every 3 months, recommended by NKF-DOQI guidelines [5,6].

Theoretically, the duration between the two maintenance doses should be verified in each specific patient. However, this is difficult to be performed in routine practice. From the present study, the value of the initially approximate duration, is 15 days or about 2 weeks. This would be more beneficial in clinical practice. The appropiate duration would then be more easily adjusted for each specific patient.

In conclusion, the initially approximate interval between the two maintenance doses of intravenous iron therapy is about 2 weeks in erythropoietin-treated hemodialysis patients.

Acknowledgement

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Referrences

1. Macdougall IC. Poor response to erythropoietin should be fully investigated and treated. BMJ 1995; 310: 1424-5.
2. Eachbach JW, Adamson JW. Recombinant human erythropoietin: Implications for nephrology. Am J Kidney Dis 1989; 11: 203-9.
3. Sunder-Plassmann G, Horl WH. Importance of iron supply for erythropoietin therapy. Nephrol Dial Transplant 1995; 10: 2070-6.
4. National Kidney Foundation-Dialysis Outcomes Quality Initiative: NKF-DOQI clinical practice guidelines for the treatment of anemia of chronic renal failure. Am J Kidney Dis 1997; 30(Suppl 3): S192-240.
5. Frankenfield D, Johnson CA, Wish JB, Rocco MV, Madore F, Owen WF. Anemia management of adult hemodialysis patients in the U.S. : results from the 1997 ESRD core indicators project. Kidney Int 2000; 57(2): 578-89.
6. National Kidney Foundation. K/DOQI Clinical practice guidelines for anemia of chronic kidney disease. Am J Kidney Dis 2000; 37: S182-238.
7. Daugirdas JT. Second generation logarithmic estimates of single-pool variable volume Kt/V: An analysis of error. J Am Soc Nephrol 1993; 4: 1205-13.
8. Silverberg DS, Iaina A, Peer G, Kaplan E, Levi BA, Frank K, Steinbruch S, Blum M. Intravenous iron supplementation for the treatment of the anemia of moderate to severe chronic renal failure patients not receiving dialysis. Am J Kidney Dis 1996; 27: 234-8.
9. Silverberg DS, Blum M, Peer G, Kaplan F, Iaina A. Intravenous ferric saccharate as an iron supplement in dialysis patients. Nephron 1996; 72: 413-7.
10. Suh H, Wadhwa NK. Iron dextran treatment in peritoneal dialysis patients on erythropoietin. Adv Perit Dial 1992; 8: 464-6.
11. Macdougall IC, Tucker B, Thompson J, Tomson CRV, Baker LRI, Raine AEG. A randomized controlled study of iron supplementation in patients treated with erythropoietin. Kidney Int 1996; 50: 1694-9.
12. Taylor JE, Peat N, Porter C, Morgan AG. Regular, low dose intravenous iron therapy improves response to erythropoietin in hemodialysis patients. Nephrol Dial Transplant 1996; 11: 1079-83.
13. Granolleras C, Oules R, Branger B, Fourcade J, Shaldon S. Iron supplementation of hemodialysis patients receiving recombinant human erythropoietin therapy, in Bauer C, Koch KM, Scigallap, Wieczorek L (eds): Erythropoietin: Molecular physiology and clinical applications. New York, NY, Marcel Dekker, 1993: 211-8.
14. Sepandj F, Jindal K, West M, Hirsch D. Economic

appraisal of maintenance parenteral iron administration in treatment of the anemia in chronic hemodialysis patients. Nephrol Dial Transplant 1996; 11: 319-22.

การให้เหล็กทางเส้นเลือดดำในผู้ป่วยฟอกเลือด

สุวัฒนชัย เนื้อนวลสุวรรณ, อัษฎาศ์ ลีฬหวนิชกุล, พงศ์ศักดิ์ พันธุ์สิน, สมชาย เอี่ยมอ่อง

วัตถุประสงค์: *การศึกษาวิธีการให้ธาตุเหล็กทางหลอดโลหิตดำในผู้ป่วยฟอกเลือดที่ได้รับฮอร์โมนอีรีโทรพอยอีติน*
วัสดุและวิธีการ: *ทำการศึกษาในผู้ป่วย 20 ราย ที่มีค่า าทีแซทำ ต่ำกว่า 20 เปอร์เซ็นต์*
ผลการศึกษา: *ภายหลังได้รับธาตุเหล็กปริมาณ 1,000 มก.ครั้งที่ 1 ค่า าทีแซทำ เพิ่มขึ้นจาก 16.4 ± 0.5 เป็น 29.3 ± 2.6 เปอร์เซ็นต์ (P<0.05) ค่าดังกล่าวลดลงเหลือ 16.2 ± 1.4 เปอร์เซ็นต์ (P<0.05) ภายในระยะเวลา 155.6 ± 29.3 วัน เมื่อให้ธาตุเหล็กปริมาณ 1,000 มก. ครั้งที่ 2 ค่า าทีแซทำ เพิ่มขึ้นเป็น 33.7 ± 3.9 เปอร์เซ็นต์ ผู้ป่วยได้รับธาตุเหล็กขนาด 100 มก. ทุก 15.6 ± 2.9 วัน ซึ่งมีค่าเท่ากับหนึ่งส่วนสิบของระยะเวลาระหว่างการให้ธาตุเหล็ก 1,000 มก. ทั้งสองผู้ป่วยมีค่า าทีแซทำ เท่ากับ 38.5 ± 5.4, 37.1 ± 0.2, 34.2 ± 3.6, 34.1 ± 3.3, 35.3 ± 4.1 และ 36.5 ± 3.1 เปอร์เซ็นต์ ที่เวลา 1, 2, 3, 4, 5 และ 6 เดือนตามลำดับ*
สรุป: *ภายหลังการให้ธาตุเหล็กทางหลอดโลหิตดำขนาด 1,000 มก. แก่ผู้ป่วยฟอกเลือดที่ได้รับฮอร์โมน อีรีโทรพอยอีติน พบว่า การให้ธาตุเหล็กทางหลอดโลหิตดำขนาด 100 มก. ทุก 2 สัปดาห์ สามารถคงค่า าทีแซทำ สูงกว่า 20 เปอร์เซ็นต์*