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Original Article

Iron deficiency anemia and levels of oxidative stress induced by treatment modality

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Abstract ***Background***: The effects of iron deficiency anemia (IDA) and its treatment on plasma total antioxidant capacity (TAOC) were investigated.

Methods: Sixty patients with IDA and 20 healthy controls were divided into four subgroups: an oral (per os: PO) group ($n = 20$); an intramuscular (IM) group ($n = 20$); an intravenous (IV) group ($n = 20$); and the control group ($n = 20$). Blood samples were obtained from all patients before treatment, and at 24 h, 7 days, 6 and 13 weeks after initiation of IDA therapy.

Results: TAOC in the IDA group was low when compared with the control group ($P < 0.001$). Although TAOC at 24 h in the PO group was not different from the control group, the TAOC in the IM and IV groups was relatively lower ($P < 0.001$). The TAOC in the PO group at 7 days, and at 6 and 13 weeks was closest to the control group level. The mean TAOC in the IV group at 13 weeks was clearly lower relative to the PO and IM groups.

Conclusions: Oxidative stress was minimally induced with oral therapy, while IM and IV therapies induced higher levels of oxidative stress, in increasing order of intensity.

Key words intramuscular, intravenous, iron deficiency anemia, oral, total antioxidant capacity, treatment.

Iron deficiency anemia (IDA) is an important health-care problem in developing countries.[1] Because long-standing IDA in children impairs growth and mental development, early diagnosis and treatment are important in the management of IDA. Iron complexes in the form of inorganic compounds (metalloenzymes) have important functions in the organism, while their ionized forms have potential deleterious effects. Ferrous ions form free radicals, leading to cellular damage. In states of iron deficiency, synthesis of compounds containing active iron ions decelerates, and iron toxicity and even death might ensue in the case of surplus iron deposition in excess of iron storage capacity.[2] Repeated intravenous (IV) iron treatment for hemodialysis patients has been associated with signs of increased oxidative DNA injury. Elevated iron level may contribute to neuronal degeneration through excessive intracellular calcium increase caused by iron-induced oxidative stress. Excess iron intake has deleterious effects due to induction of direct intestinal damage, oxidative stress, cell toxicity, endothelial dysfunction or growth of pathogens.[3–5]

Utilization of iron compounds that are pre-oxidant molecules might enhance oxidative stress in the body.[2] Oxidative stress is related to cardiovascular and infectious diseases, cancer, diabetes and neurodegenerative pathology. IDA can affect the oxidant–antioxidant system. These changes can be corrected with iron therapy.[6]

The measurement of total antioxidant capacity (TAOC) considers the cumulative action of all the antioxidants present in plasma and body fluids, thus providing an integrated parameter rather than the simple sum of measurable antioxidants. The capacity of known and unknown antioxidants and their synergistic interaction is therefore assessed, thus giving an insight into the delicate balance *in vivo* between oxidants and antioxidants. Measurement of plasma TAOC may help in the evaluation of physiological, environmental, and nutritional factors of the redox status in humans. Determination of plasma TAOC may help to identify conditions affecting oxidative status *in vivo*.[7]

To date, the effects of IDA and its treatment on TAOC have not been studied. The aim of the present study was to determine the impact of IDA and its treatment on plasma TAOC level. The intent was to introduce a new perspective for the preferred mode of iron dosing.

Methods

The study enrolled 60 IDA patients and 20 subjects as a healthy control group. The patients were divided into three treatment groups: the oral (per os: PO) group ($n = 20$; group 1); the intramuscular (IM) group ($n = 20$; group 2); and the IV group ($n = 20$; group 3); the 20 healthy subjects comprised the control group ($n = 20$; group 4). Treatment groups were randomly selected. As an oral iron therapy ferrous sulfate (Ferro-Sanol® syrup, Adeka

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Pharm, Samsun, Turkey) at a dose of 4–6 mg/kg was given for 3 months. For IM treatment, ferro III hydroxy polymaltose (Ferrum Haussman® ampoule; Abdi Ibrahim Pharm., Istanbul, Turkey) was used. IM iron therapy was given on alternate days at an average dose of 5.9 ± 3.8 mg/kg (between 3 and 15 days of therapy), and then maintained at a dose of 12.8 ± 4.3 mg/kg per day (3.2–24.6 mg/kg per dose). For IV treatment, iron sucrose (Venofer® ampoule Abdi Ibrahim Pharm.) was used. For IV iron therapy the patients were hospitalized. The patients received diphenhydramine, and acetaminophene 30 min before IV iron therapy. The patients were closely monitored during IV infusion therapy, which was given on alternate days. According to treatment protocol, 20 mg/mL IV iron solution was added into 75–100 mL physiologic saline, and infused in 2 h at a rate of 13.8 ± 6.2 mg/kg (4–26 mg/kg per dose). The solution was infused at a slower rate within the first 10 min to check for a potential adverse reaction. Dosage of parenteral iron (IM, IV) was calculated according to the formula based on Hb level and children's bodyweight at the time of the diagnosis.[8,9]

$$\text{Total dosage of iron (mg)} = (\text{required Hb} - \text{observed Hb}) \times 80\ \text{mL} \times \text{bodyweight (kg)} \times 0.034$$

$$\text{Absolute total dose of IV iron (mg)} = \text{Total dose of iron} + 20\%\ (\text{total dosage of iron})$$

A total of 80 mL blood volume was used per kilogram of bodyweight with a correction factor of 0.034. To replenish iron stores, 20% was added to the total amount. According to the Hb level, 20 mg/mL iron supplement in 75–100 mL 0.9% NaCl solution was given IV at an average rate of 13.8 ± 6.2 mg/kg per dose (range: 4–26 mg/kg per dose) over 2 h. Infusion rates were slowed within the first 10 min. The infusions were completed within 2–3 days.[8,9]

Blood samples were taken from all patients, immediately before treatment, and at 24 h, 7 days, 6 and 13 weeks after treatment.[6,10,11] Whole blood samples obtained were analyzed for iron (Fe) concentration, total iron binding capacity and ferritin, while ethylenediamine tetra-acetic acid (EDTA) was added into the tubes containing whole blood samples. For the estimation of total blood count, blood samples drawn for TAOC were transferred into heparinized tubes, their plasma portions were separated and stored in deep freeze at −80°C for 2 months. The Erel method was used for the measurement of TAOC.[12]

The results obtained were evaluated using SPSS for Windows (SPSS, Chicago, IL, USA), and expressed as mean ± SD. One-way analysis of variance (ANOVA) and then Tukey's B and Scheffe tests were used for intergroup, and intragroup comparisons of treatment modalities, respectively. Pearson's correlation test was used to compare intragroup comparisons of parameters used. $P < 0.05$ was accepted as statistically significant.

Results

Demographic subject characteristics are listed in Table 1. Any statistically significant difference among treatment groups with respect to Hb was not detected ($P > 0.05$). Increase in Hb level at 7 days in the IV group was greater than for the PO group ($P = 0.001$). Only in the PO group was Hb at 13 weeks found to be similar to that of the control group (Table 2).

In the IV group, ferritin at 24 h was significantly increased according to the PO and IM groups ($P < 0.001$; Table 3).

In the IDA groups, TAOC was found to be lower when compared with the control group ($P < 0.001$). At 24 h, TAOC in the PO group was not different from the control group ($P > 0.05$), while the TAOC in the IM and IV groups was relatively lower ($P < 0.001$).

The TAOC at 7 days in the PO, IM and IV groups ($P < 0.05$) was significantly lower than that of the control group ($P < 0.001$). At 7 days in the PO group TAOC was significantly higher than the IM ($P < 0.05$) and IV ($P < 0.001$) groups. At 6 weeks TAOC was highest in the PO and lowest in the IV groups.

At 24 h, 1, 6 and 13 weeks, the TAOC in the PO group was significantly higher than in the IV group.

At 13 weeks, even though TAOC was higher in the PO group, it was significantly lower than the control group (Table 4; Fig. 1)

Discussion

Oral iron therapy is the first preferred dosage route in children. Parenteral (IM, IV) iron therapy has no advantage over oral therapy except for shorter treatment duration. Oral iron therapy, however, might prove to be inadequate in malabsorptive disorders hindering absorption of oral iron, in conditions in which rapid response is required such as in preoperative preparation; in cases of intolerance to oral iron therapy despite attempts at dose adjustment; in patients in whom oral iron therapy is exacerbating symptoms of underlying chronic inflammatory bowel disease; in severe iron deficiency anemia, maintenance of treatment in noncompliant children; in cases of chronic and intractable bleeding; acute diarrhea; insufficient absorption of iron because of iatrogenic and gastrointestinal etiologies; and renal failure requiring erythropoietin treatment. In such cases parenteral therapy should

Table 1 Demographic subject characteristics

	Group 1 (PO) mean ± SD (min–max)	Group 2 (IM) mean ± SD (min–max)	Group 3 (IV) mean ± SD (min–max)	Group 4 (control) mean ± SD (min–max)
Age (months)	56.35 ± 46.28 (6–144)	104.50 ± 78.66 (6–204)	62.60 ± 64.43 (7–180)	93.90 ± 53.07 (6–186)
Sex, *n* (%)				
Male	12 (60)	11 (55)	12 (60)	11 (55)
Female	8 (40)	9 (45)	8 (40)	9 (45)

IM, intramuscular; IV, intravenous; PO, per os.

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Table 2 Change in Hb with time (mean ± SD)

Groups	Before treatment (n = 20) (g/dL)	24 h (n = 20) (g/dL)	7 days (n = 20) (g/dL)	6 weeks (n = 20) (g/dL)	13 weeks (n = 20) (g/dL)	†P
Group 1 (PO)	(1) 8.02 ± 1.65	(2) 8.15 ± 1.60	(3) 8.22 ± 1.25	(4) 11.68 ± 0.77	(5) 12.77 ± 0.76	1–4 $P < 0.001$ 1–5 $P < 0.001$ 2–4 $P < 0.001$ 2–5 $P < 0.001$ 3–4 $P < 0.001$ 3–5 $P < 0.001$
Group 2 (IM)	(6) 8.13 ± 1.45	(7) 8.11 ± 1.73	(8) 9.41 ± 1,53	(9) 11.07 ± 1.35	(10) 11.82 ± 0.95	6–9 $P < 0.001$ 6–10 $P < 0.001$ 7–9 $P < 0.001$ 7–10 $P < 0.001$ 8–9 $P < 0.05$ 8–10 $P < 0.001$
Group 3 (IV)	(11) 7.51 ± 1.80	(12) 7.68 ± 1.73	(13) 9.46 ± 1.36	(14) 11.41 ± 0.82	(15) 12.22 ± 0.97	11–13 $P = 0.001$ 11–14 $P < 0.001$ 11–15 $P < 0.001$ 12–14 $P < 0.001$ 12–15 $P < 0.05$ 13–14 $P = 0.001$ 13–15 $P < 0.001$
Group 4 (control)	(16) 13.22 ± 0.67					
‡P	1–16 $P < 0.001$ 6–16 $P < 0.001$ 11–16 $P < 0.001$	2–16 $P < 0.001$ 7–16 $P < 0.001$ 12–16 $P < 0.001$	3–8 $P < 0.05$ 3–13 $P < 0.05$ 3–16 $P < 0.001$ 8–16 $P < 0.001$ 13–16 $P < 0.001$	9–16 $P < 0.001$ 14–16 $P < 0.001$	5–10 $P = 0.001$ 10–16 $P = 0.001$ 15–16 $P < 0.001$	

†Statistically different according to treatment days; ‡statistically different between different therapy groups. IM, intramuscular; IV, intravenous; PO, per os.

be instituted in order to replenish iron stores rapidly and efficiently.[8,9] In the present study a difference in Hb level was detected between that before treatment and after 6 weeks of PO and IM therapy. In the IV group a difference was noted between the pretreatment level and that at 7 days after the therapy had started ($P = 0.001$; Table 2). Because any increase in level is not seen before 7 days of therapy, IV iron therapy is not indicated for rapid Hb elevation.

Only a scant number of studies related to parenteral and especially IV iron therapy have been conducted in IDA. This therapy has been used in children for whom long-term treatment is impossible for sociocultural reasons. Use of parenteral therapy is restricted due to its adverse effects. IV iron therapy is more expensive than oral therapy in that it requires hospitalization, close monitoring by health-care personnel, and availability of infusion sets. IM injections result in increase in necrosis of muscular tissue, cutaneous spots and injection site pain. Duration of treatment is also relatively longer. To date, no carcinogenic events have been reported after long-term IM iron therapy. Occurrence of rhabdomyolysis has been noted after long-term iron therapy. Owing to these factors, IV therapy was preferred over IM therapy.[8,9,13] None of the present patients developed any complications.

The human body has a complex defense system to fight against oxidative stress.[2] It is recognized that iron would result in the formation of OH^- radicals, mediated by Fenton and Haber–Weiss reactions and also contribute to the formation of lipid hydroperoxide (LPO). Therefore, excess use of iron should be avoided.[14] In the present study the difference between TAOC level in the IV and IM groups, in which patients were given higher doses of iron, and the PO group, in which patients were given lower doses of iron gradually, were investigated.

The percent contributions of the parameters of serum TAOC are proteins (49%), vitamin C (5%), and bilirubin (1.69%). Albumin, uric acid, and vitamin C comprise >85% of TAOC. Quantitative analysis of TAOC provides more valuable information than measurements of antioxidants per se. The cumulative effects of all antioxidants found in plasma and body fluids are reflected in TAOC.[7,12]

A limited number of studies have investigated oxidative stress and antioxidant defense mechanisms. Alterations in antioxidant state as a result of iron therapies via different dosage routes have not been elucidated fully. The absorption process after parenteral iron might last for at least 4 weeks and thus the generation of free radicals might be prolonged.[15–20] Therefore in the present study the patients were followed until 13 weeks after termination of oral iron therapy, and blood samples were collected to measure these alterations.

A decrease in the antioxidant capacity of red blood cells (RBC) and increase in LPO have been demonstrated.[15,16] Studies are also available on the similarities between superoxide dismutase (SOD) and catalase (CAT) activities, increases in SOD, and decreases in activities of antioxidant enzymes such as SOD, glutathione peroxidase (GSH-Px) and CAT in IDA.[15,16] RBC are more sensitive to oxidation. In the present study the TAOC level

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Table 3 Change in ferritin with time

Groups	Before treatment ($n = 20$) (ng/mL, mean ± SD)	24 h ($n = 20$) (ng/mL, mean ± SD)	7 days ($n = 20$) (ng/mL, mean ± SD)	6 weeks ($n = 20$) (ng/mL, mean ± SD)	13 weeks ($n = 20$) (ng/mL, mean ± SD)	†*P*
Group 1 (PO)	(1) 9.11 ± 5.60	(2) 12.37 ± 6.97	(3) 16.18 ± 6.72	(4) 25.67 ± 13.72	(5) 36.65 ± 16.32	1–4 $P < 0.001$ 1–5 $P < 0.001$ 2–4 $P < 0.01$ 2–5 $P < 0.001$ 3–5 $P < 0.001$ 4–5 $P < 0.05$
Group 2 (IM)	(6) 6.72 ± 4.06	(7) 46.73 ± 20.88	(8) 50.81 ± 28.41	(9) 30.43 ± 19.81	(10) 15.15 ± 7.98	6–7 $P < 0.001$ 6–8 $P < 0.001$ 6–9 $P < 0.01$ 7–10 $P < 0.001$ 8–9 $P < 0.05$ 8–10 $P < 0.001$
Group 3 (IV)	(11) 6.75 ± 3.44	(12) 102.63 ± 47.59	(13) 123.84 ± 76.08	(14) 37.15 ± 19.94	(15) 24.13 ± 14.08	11–12 $P < 0.001$ 11–13 $P < 0.001$ 12–14 $P < 0.001$ 12–15 $P < 0.001$ 13–14 $P < 0.001$ 13–15 $P < 0.001$
Group 4 (control)	(16) 42.29 ± 22.11					
‡*P*	1–16 $P < 0.001$ 6–16 $P < 0.001$ 11–16 $P < 0.001$	2–7 $P < 0.001$ 2–12 $P < 0.001$ 2–16 $P < 0.001$ 7–12 $P < 0.001$ 7–16 $P < 0.001$	3–8 $P < 0.001$ 3–13 $P < 0.001$ 3–16 $P < 0.001$ 8–13 $P < 0.001$ 13–16 $P < 0.001$	4–16 $P < 0.01$	5–10 $P = 0.01$ 5–15 $P < 0.001$ 10–16 $P < 0.01$ 15–16 $P < 0.001$	

†Statistically different according to treatment days; ‡statistically different between different therapy groups. IM, intramuscular; IV, intravenous; PO, per os.

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Table 4 Change in TAOC with time (mean ± SD)

Groups	Before treatment (n = 20) (mmol trolox eq/L)	24 h (n = 20) (mmol trolox eq/L)	7 days (n = 20) (mmol trolox eq/L)	6 weeks (n = 20) (mmol trolox eq/L)	13 weeks (n = 20) (mmol trolox eq/L)	†P
Group 1 (PO)	(1) 1.71 ± 0.26	(2) 2.04 ± 0.24	(3) 1.98 ± 0.26	(4) 1.86 ± 0.20	(5) 1.92 ± 0.30	1–2 $P < 0.01$
						1–3 $P < 0.05$
Group 2 (IM)	(6) 1.79 ± 0.25	(7) 1.72 ± 0.28	(8) 1.84 ± 0.13	(9) 1.81 ± 0.16	(10) 1.87 ± 0.10	NS
Group 3 (IV)	(11) 1.77 ± 0.14	(12) 1.67 ± 0.19	(13) 1.64 ± 0.22	(14) 1.56 ± 0.37	(15) 1.71 ± 0.15	NS
Group 4 (control)	(16) 2.15 ± 0.19					
‡P	1–16 $P < 0.001$	2–7 $P < 0.001$	3–8 $P < 0.05$	4–14 $P < 0.01$	5–15 $P < 0.01$	
	6–16 $P < 0.001$	2–12 $P < 0.001$	3–13 $P < 0.001$	4–16 $P < 0.001$	5–16 $P < 0.01$	
	11–16 $P < 0.001$	7–16 $P < 0.001$	3–16 $P < 0.05$	9–14 $P = 0.01$	10–15 $P = 0.001$	
		12–16 $P < 0.001$	8–13 $P < 0.01$	9–16 $P < 0.001$	10–16 $P < 0.001$	
			8–16 $P < 0.001$	14–16 $P < 0.001$	15–16 $P < 0.001$	
			13–16 $P < 0.001$			

†Statistically different according to treatment days; ‡statistically different between different therapy groups. IM, intramuscular; IV, intravenous; PO, per os; TAOC, total antioxidant capacity.

Fig. 1 Total antioxidant capacity (mmol trolox eq/L) vs time and treatment modality. ■, group 1 (per os); ▤, group 2 (intramuscular); ▥, group 3 (intravenous); □, control.

was lower in the IDA groups than in the control group (Table 4). The reason for this phenomenon could be the lowering of plasma levels of iron-containing antioxidant enzymes and development of oxidative stress because of hypoxia in patients with IDA.[15,16]

Kurtoglu *et al*. found decreases in oxidative stress markers (malondialdehyde, GSH-Px, SOD and CAT) relative to controls after iron therapy.[11] Any significant difference was not observed between 6 weeks and the end of the treatment. This suggests simultaneous normalization of both Hb level and the oxidant–antioxidant balance. In the present treatment groups, however, there was no significant difference in TAOC between the pre-treatment value and that at 6 weeks and 13 weeks (end-treatment) of iron therapy (Table 4).

After replenishment of stores, free iron can lead to toxic effects. Experimental studies have shown that iron ions cause oxidative stress and readily lead to membrane damage. Studies have established that IV delivery of iron gluconate used for patients with hemodialysis does not induce peroxidation. In the present IV group serum iron and ferritin levels at 24 h after initiation of therapy were found to be considerably higher compared with the other two groups (Table 3). Oxygen reduction products and higher amounts of iron ions are indicative of cellular exposure to oxidant stress.[21] Akasaka and Yamamoto noted development of mutations in DNA sequences obtained when the pZ189 plasmid of *Escherichia coli* was treated with Fe^{+2}/EDTA.[22]

Sozmen *et al*. did not find any toxic effect of ferrous formulations on RBC and plasma in pediatric IDA patients.[17] In the present study, TAOC level increased promptly in the PO group, while oxidative stress peculiar to IDA decreased.

No significant differences were found between groups with regard to mean subject age ($P > 0.05$; Table 1). Patient age has an effect on TAOC level. In infants with neonatal icterus, higher serum TAOC level has been detected as compared with age-matched healthy infants.[12,23]

McAnulty *et al*. started iron therapy in non-anemic patients whose iron stores were normal or somewhat depleted.[23] Serum concentrations of selenium and GSH-Px were not different between these two groups. In a similar group of patients, Gropper

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et al. did not find any association between oral iron therapy and oxidative damage.[18] In the present study, before treatment the TAOC level in the three IDA groups (PO, IM, and IV) was found to be lower than the control group (Table 4). No statistically significant increase in TAOC level after PO therapy was found. Thus it is possible to conclude that, such as with too much iron, IDA adversely affects TAOC level permanently. In the present study, PO and IM therapy reduced oxidative stress in decreasing order of intensity. IV therapy for IDA induces a much higher level of oxidative stress. In none of the treatment groups was end-treatment TAOC identical to normal TAOC found in the control group. Normal TAOC level was achieved at 24 h in the PO group.

Rehema *et al*. found that lower doses of ferrous formulations did not induce significant changes in oxidative stress parameters (TAOC, total GSH, glutathione disulfide, carbonyl protein, CAT, and lower density lipoproteins) in healthy pregnant women with borderline IDA.[24] In the present study, however, higher TAOC level was detected in the PO group as compared with the IV and IM groups, in which higher doses of iron were given rapidly (Table 4). This indicates that in the long term the level of oxidative stress is lower during PO therapy utilizing lower doses of iron. Iron has been proposed to promote oxidative stress and endothelial dysfunction in vascular tissues. This potential mechanistic link between IV iron and endothelial dysfunction warrants further study of the cardiovascular effects of IV iron in anemic subjects.[25]

Maximum tolerated single dose of IV iron infusion and iron pharmacokinetics are not known in children and not clear in adults. Systemic iron toxicity was found in a child infused with 16 mg/kg IV iron sucrose for 3 h.[19] In the present study no problem was encountered even with IV infusions of 26 mg/kg doses; and a considerable (although not statistically significant) difference in Hb level was seen between the IV and IM groups. Although no complications were observed in the present IV and IM groups, oxidative stress was relatively common during parenteral (IV and IM) iron therapy, as shown in the present study.

Parenteral iron therapy is suggested to lead to an increase in the intracellular concentration of free iron ions and a resultant augmentation of free radical formation.[15] In the present study, before treatment the TAOC level in the three IDA groups (PO, IM, and IV groups) was found to be lower than the control group (Table 4). It was concluded that higher levels of oxidative stress were prevalent in IDA. According to the route of iron therapy dosage, minimal oxidative stress was detected during PO, and then the IM and IV routes in increasing order of intensity. Oxidative stress related to IV therapy can be reduced by decreasing the number of doses and prolonging dose intervals.

In hemodialysis patients, IV iron sucrose therapy does not elevate malondialdehyde in plasma and RBC. In some studies IV iron sucrose was found to enhance oxidation of albumin, leading to increase in plasma protein carbonyl content. IV iron sucrose and iron gluconate were found to increase oxidative stress.[10,20] Thirteen weeks after a single 0.5 g/kg IV iron dextran injection into rats with chronic renal failure, oxidative stress was enhanced and levels of antioxidant enzymes decreased.[11] In the present IV group, TAOC level at every stage of the therapy was comparatively lower. At every stage of PO and IM therapy, TAOC increased above IDA levels. In the IV group, however, TAOC fell to below the threshold of IDA diagnostic criteria.

The easy-to-use oral route is the most prevalent mode of dosage for iron therapy; it is efficient and produces relatively milder adverse reactions. Parenteral iron therapy (IM, IV) has no advantage over oral therapy except for shorter duration of treatment. In cases in which oral therapy is not feasible, IM and especially IV iron therapy affect oxidative state adversely. Induction of oxidative stress is at its lowest with oral therapy, then with IM and IV therapies in increasing order of intensity. If absolute indications do not exist for IV iron therapy, then, especially in children, this form of treatment is contraindicated owing to the development of oxidative stress sequelae in later life.

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