ONE MINUTE CONSULT

BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Is iron therapy for anemia harmful in the setting of infection?

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There are no irrefutable data on harm, but none on benefit either

A: The harmful effects of iron therapy in the setting of infection are more theoretical than observed, with no irrefutable data to support them. On the other hand, there are also no convincing data to support the benefit of this therapy. If iron is to be used, frequent monitoring of serum iron markers is prudent to avoid iron overload during treatment.

ANEMIA OF INFLAMMATION IS COMPLEX

Anemia that develops in the hospital, especially in the setting of infection or inflammation, is similar hematologically to anemia of chronic disease, except for its acute onset.[1]

The pathogenesis of anemia in such settings is complex, but the most important causes of this common syndrome include shortening of red cell survival, impaired erythropoietin production, blunted responsiveness of the bone marrow to endogenous erythropoietin, and impaired iron metabolism mediated through the action of inflammatory cytokines.[2,3] Other important causes include nutritional deficiencies (iron, vitamin B_{12}, and folic acid)[4] and blood loss.[5,6]

Moreover, anemia of inflammation may be difficult to differentiate from iron-deficiency anemia because the serum iron markers are unreliable in inflammation.[1]

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The reported prevalence of anemia during hospitalization has ranged from 55% on hospital wards[7] to 95% in intensive care units.[8]

Transfusion of packed red blood cells is the fastest treatment for anemia in hospitalized patients and it is the one traditionally used, but many concerns have been raised about its efficacy and adverse effects.[9] Erythropoietin, with or without iron therapy, has emerged as an alternative in treating anemia of inflammation.[10,11]

IRON THERAPY

Iron is widely used to treat anemia, especially in hospitalized patients and those with chronic kidney disease.[2] The intravenous route is more commonly used than the oral route, since it has faster action, is better tolerated, and has better bioavailability.[1,2]

Controversy over benefit

Whether iron supplementation increases the red blood cell mass and reduces the need for blood transfusion is controversial.[10,12] Pieracci et al[13] documented these benefits in critically ill surgical patients, whereas van Iperen et al[11] did not find such benefits in critically ill patients receiving intravenous iron and erythropoietin.

Harmful effects

Some authors[1,14] object to giving iron to hospitalized patients (especially critically ill patients) who have infections on the grounds that it is risky, although definitive evidence is lacking.[15]

Most of the harmful effects of iron have been linked to elevated serum ferritin levels and to non–transferrin-bound iron, more than

to iron per se.[16] Ferritin is an acute-phase reactant; thus, ferritin levels may be elevated in inflammation and infection regardless of the body iron status.[1]

Anaphylactic reaction. This rare complication of iron dextran therapy is not much of a concern at present with the newer formulations of iron such as iron gluconate and iron sucrose.[16]

Oxidative stress. Iron-derived free radicals can cause a rise in inflammatory cytokine levels, especially if the ferritin level is elevated (> 500 µg/L). This cytokine rise is worrisome, as it may have acute detrimental effects on cellular homeostasis, leading to tissue injury,[15] while chronically it might be related to enhanced atherosclerosis and cardiac disease.[16]

Iron overload. In vitro and animal studies have documented an association between elevated ferritin levels (500–650 µg/L) and decreases in T-cell function, polymorphonuclear neutrophil migration, phagocytosis, and bacterial eradication.[15] Studies in hemodialysis patients have identified iron overload as an independent risk factor for bacterial infection, but the confounding role of the dialysis process cannot be disregarded.[17,18]

Bacterial growth. Many bacteria depend on iron for their growth; examples are *Escherichia coli*; *Klebsiella*, *Pseudomonas*, *Salmonella*, *Yersinia*, *Listeria*, and *Staphylococcus* species; and *Haemophilus influenzae*. In vitro studies have linked increased bacterial growth with increased transferrin saturation in plasma.[15,19]

Iron therapy and infection risk

The theory linking iron with risk of infection arose from the observation that patients with hemochromatosis are more susceptible to certain bacterial infections, especially *Vibrio vulnificus*.[20] A few human studies, most of them in chronic hemodialysis patients, have examined the relation between iron therapy and infection risk, with conflicting results.[21–26] Multiple studies[13,19,21,22,25–27] found no relation between iron therapy and risk of infection or death.

Canziani et al[23] found that the risk of infection was higher with higher intravenous doses of iron than with lower doses.

Collins et al[24] found a higher risk of sepsis and hospitalization in patients who received iron for a prolonged duration (5–6 months) than in those who did not.

Feldman et al,[27] in their report of a study of iron therapy in hemodialysis patients, suggested that previously observed associations between iron administration and higher death rates may have been confounded by other factors.

Iron therapy in concurrent infection

There are no data in humans on the effects of iron therapy on outcomes during concurrent infection or sepsis.[15,28] However, mice with sepsis had worse outcomes when treated with intravenous iron.[28]

A CONUNDRUM IN CLINICAL PRACTICE

After reviewing the available literature, we concur with most of the authors[1,15,16,18,19,29] that despite the worrisome theoretical adverse effects of iron therapy in patients with infections, there are no convincing data to support those fears. On the other hand, there are also no convincing data to favor its benefit.

If iron is used, frequent monitoring of serum iron markers is prudent

More definitive studies are needed to answer this question, which has been a conundrum in clinical practice. Patients who might benefit from iron therapy should not be deprived of it on the basis of the available data. Frequent monitoring of serum iron markers during therapy to avoid iron overload seems prudent. ■

REFERENCES

1. **Pieracci FM, Barie PS**. Diagnosis and management of iron-related anemias in critical illness. Crit Care Med 2006; 34:1898–1905.
2. **Krantz SB**. Pathogenesis and treatment of the anemia of chronic disease. Am J Med Sci 1994; 307:353–359.
3. **Price EA, Schrier SL**. Unexplained aspects of anemia of inflammation. Review article. Adv Hematol 2010; 2010:508739.
4. **Rodriguez RM, Corwin HL, Gettinger A, Corwin MJ, Gubler D, Pearl RG**. Nutritional deficiencies and blunted erythropoietin response as causes of the anemia of critical illness. J Crit Care 2001; 16:36–41.
5. **Wong P, Intragumtornchai T**. Hospital-acquired anemia. J Med Assoc Thai 2006; 89:63–67.
6. **Thavendiranathan P, Bagai A, Ebidia A, Detsky AS, Choudhry NK**. Do blood tests cause anemia in hospitalized patients? The effect of diagnostic phlebotomy on hemoglobin and hematocrit levels. J Gen Intern Med 2005; 20:520–524.
7. **Reade MC, Weissfeld L, Angus DC, Kellum JA, Milbrandt EB**. The prevalence of anemia and its association with 90-day mortality in hospitalized community-acquired pneumonia. BMC Pulm Med 2010; 10:15.
8. **Debellis RJ**. Anemia in critical care patients: incidence, etiology, impact, management, and use of treatment guidelines and protocols. Am J Health Syst Pharm 2007; 64:S14–S21.

9. **Marik PE**. The hazards of blood transfusion. Br J Hosp Med (Lond) 2009; 70:12–15.
10. **Corwin HL, Gettinger A, Fabian TC, et al**. Efficacy and safety of epoetin alfa in critically ill patients. N Engl J Med 2007; 357:965–976.
11. **van Iperen CE, Gaillard CA, Kraaijenhagen RJ, Braam BG, Marx JJ, van de Wiel A**. Response of erythropoiesis and iron metabolism to recombinant human erythropoietin in intensive care unit patients. Crit Care Med 2000; 28:2773–2778.
12. **Muñoz M, Breymann C, García-Erce JA, Gómez-Ramirez S, Comin J, Bisbe E**. Efficacy and safety of intravenous iron therapy as an alternative/adjunct to allogeneic blood transfusion. Vox Sang 2008; 94:172–183.
13. **Pieracci FM, Henderson P, Rodney JR, et al**. Randomized, double-blind, placebo-controlled trial of effects of enteral iron supplementation on anemia and risk of infection during surgical critical illness. Surg Infect 2009; 10:9–19.
14. **Pieracci FM, Barie PS**. Iron and the risk of infection. Surg Infect 2005; 6(suppl 1):S41–S46.
15. **Maynor L, Brophy DF**. Risk of infections with intravenous iron therapy. Ann Pharmacother 2007; 41:1476–1480.
16. **Cavill I**. Intravenous iron as adjuvant therapy: a two-edged sword? Nephrol Dial Transplant 2003; 18(suppl 8):viii24–viii28.
17. **Kessler M, Hoen B, Mayeux D, Hestin D, Fontenaille C**. Bacteremia in patients on chronic hemodialysis. A multicenter prospective survey. Nephron 1993; 64:95–100.
18. **Hoen B, Kessler M, Hestin D, Mayeux D**. Risk factors for bacterial infections in chronic haemodialysis adult patients: a multicentre prospective survey. Nephrol Dial Transplant 1995; 10:377–381.
19. **Cieri E**. Does iron cause bacterial infections in patients with end stage renal disease? ANNA J 1999; 26:591–596.
20. **Jurado RL**. Iron, infections, and anemia of inflammation. Clin Infect Dis 1997; 25:888–895.
21. **Brewster UC, Coca SG, Reilly RF, Perazella MA**. Effect of intravenous iron on hemodialysis catheter microbial colonization and blood-borne infection. Nephrology 2005; 10:124–128.
22. **Aronoff GR, Bennett WM, Blumenthal S, et al; United States Iron Sucrose (Venofer) Clinical Trials Group**. Iron sucrose in hemodialysis patients: safety of replacement and maintenance regimens. Kidney Int 2004; 66:1193–1198.
23. **Canziani ME, Yumiya ST, Rangel EB, Manfredi SR, Neto MC, Draibe SA**. Risk of bacterial infection in patients under intravenous iron therapy: dose versus length of treatment. Artif Organs 2001; 25:866–869.
24. **Collins A, Ma J, Xia H, et al**. I.V. iron dosing patterns and hospitalization. J Am Soc Nephrol 1998; 9:204A.
25. **Burns DL, Mascioli EA, Bistrian BR**. Effect of iron-supplemented total parenteral nutrition in patients with iron deficiency anemia. Nutrition 1996; 12:411–415.
26. **Olijhoek G, Megens JG, Musto P, et al**. Role of oral versus IV iron supplementation in the erythropoietic response to rHuEPO: a randomized, placebo-controlled trial. Transfusion 2001; 41:957–963.
27. **Feldman HI, Joffe M, Robinson B, et al**. Administration of parenteral iron and mortality among hemodialysis patients. J Am Soc Nephrol 2004; 15:1623–1632.
28. **Javadi P, Buchman TG, Stromberg PE, et al**. High-dose exogenous iron following cecal ligation and puncture increases mortality rate in mice and is associated with an increase in gut epithelial and splenic apoptosis. Crit Care Med 2004; 32:1178–1185.
29. **Lapointe M**. Iron supplementation in the intensive care unit: when, how much, and by what route? Crit Care 2004; 8(suppl 2):S37–S41.

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