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**Proactive high-dose IV iron is preferred therapy in ESKD patients: CON**

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**Key Points:**

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**Abstract:**

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Proactive high-dose IV iron is preferred therapy in ESKD patients: CON

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We would like to start the debate by affirming that there are likely several points of agreement with the “pro” high dose intravenous iron therapy. First, hemoglobin synthesis requires iron, which sits at the center of heme porphyrin ring, and allows red blood cells to transport oxygen to tissues throughout the body. Next, patients with End Stage Kidney Disease (ESKD) are highly susceptible to iron deficiency from two concurrent processes--impaired iron metabolism, and on-going blood loss. Patients with ESKD have impaired iron metabolism because of underlying inflammation, which promotes production of the liver protein hepcidin, a key regulatory protein that inhibits the transfer of iron in enterocytes, macrophages, and hepatocytes through its effect on another regulatory protein, ferroportin. The net result is reduced availability of iron for erythropoiesis. Individuals with advanced chronic kidney disease, especially persons on hemodialysis, have on-going blood loss from repeat cannulation of the access, residual blood in the dialysis circuit tubing, and frequent blood draws--leading to profound iron deficiency. Up to 7 mg of iron may be lost per hemodialysis session, totaling up to 1600 mg/year. Patients with advanced chronic kidney disease have angiodysplasia of the GI tract leading to additional blood loss. Thus, we concede that intravenous iron is likely the preferred mode of administration because oral iron is unlikely to replenish the losses. Current practice patterns confirm that most patients with ESKD regularly receive intravenous iron. Yet, dose matters, and we would argue against the use of high dose intravenous iron in ESKD for the following four reasons.

**Reason #1**

*High dose intravenous iron may contribute to labile iron formation*

All current formulations of intravenous iron also have a carbohydrate shell surrounding a core of iron that shifts between the ferrous and ferric state. After administration, intravenous iron bypasses enteric absorption and goes directly to the cells of the reticuloendothelial system within the liver and spleen; a large majority of the iron goes to the liver because of its high blood flow relative to the spleen. The iron is transferred slowly into the marrow by an intermediate step of binding to transferrin, which then delivers the iron to the marrow. The time course of transfer after administration is important--the uptake of iron sucrose into the liver and the spleen is
nearly complete within one to two hours, and then transferred to the marrow. Yet, specialized magnetic resonance imaging of individuals with chronic kidney disease and ESKD reveal that the liver sequesters the iron for long periods, sometimes well over 3 months.\(^4\)

Homeostatic pathways in the body handle 20-25 mg of iron daily. Currently, typical doses of intravenous iron include the following: iron sucrose 25 to 100 mg per dose, ferric gluconate 62.5 mg to 125 mg per dose, ferumoxytol 510 mg per dose, and ferric carboxymaltose 750 mg per dose. Even at relatively low doses, the absolute quantity of administered intravenous iron largely surpasses the quantity that is routinely handled by the hemostatic pathways.

The potentially large amount of excess iron may serve as a pool for the development of labile iron when it exceeds to carrying capacity of transferrin. Labile iron can participate in the generation, via the Fenton reaction\(^5\), of harmful radicals that oxidize lipids and DNA. In this way, excess iron may contribute to accelerated atherosclerosis, and eventually clinical cardiovascular disease.

**Reason #2**

*What constitutes high dose intravenous iron is not well defined*

In this debate regarding the use of high dose intravenous iron, it is important to clearly define what constitutes high dose due to the great variation that exists in practice across the clinics worldwide. In many countries, but especially the United State, high dose has been generally synonymous with dosing practices often called “bolus” that administer up to 1000 mg per month, often over consecutive hemodialysis sessions; low dose has been considered as dosing practices often called “maintenance” that administer less than 200 mg per month, typically divided equally into weekly allotments. Since the publication of the recent PIVOTAL (Proactive IV IrOn Therapy in HaemodiAlysis Patients) trial,\(^6\) a proactive repletion strategy is becoming synonymous with high dose intravenous iron. In PIVOTAL, patients assigned to the proactive regimen received a median monthly dose of 264 mg (maximum of 400 mg). However, this dosing regimen differs from the common practice in the US. Currently in the US, at
least 40% of dialysis clinics administer ≥ 250 mg per month (20% averaging ≥ 500mg) with marked variation by facility size and profit status.²

A more precise definition of high dose intravenous iron should also incorporate frequency of dosing and dynamic laboratory parameters. For example, administration of 100 mg of intravenous iron consecutively for 10 hemodialysis sessions and administration of 250 mg once weekly for 4 weeks would both total 1000 mg in a month; however, duration of time between doses and the absolute amount given per dose may result in differential metabolism. Furthermore, clinicians use laboratory parameters such as transferrin saturation, ferritin, and hemoglobin levels to make decisions on iron administration. Administration of proactive iron dosing in the PIVOTAL trial was terminated at a serum ferritin value of >700ug/L or transferrin saturation of ≥40%,⁶ which are lower than thresholds commonly used in US clinical practice. Yet, currently there is lack of consensus for initiation and termination recommendations for intravenous iron therapy with different cutoffs recommended by different organizations including Kidney Disease Global Outcomes, European Renal Best Practices, Kidney Disease Outcome Quality Initiative, Canadian Society of Nephrology, Kidney Health Australia, and the National Institute for Health and Care Excellence.⁷

In our opinion, the net effect of the varying definitions of high dose intravenous iron is that it limits our ability to make valid conclusions on its safety and efficacy relative to other dosing approaches because we do not know what constitutes high dose. The proactive dose is not synonymous with high dose. Extrapolating the safety and efficacy profile of the proactive dosing approach to all high dose intravenous iron is not appropriate.

Reason #3
The benefits of high dose intravenous iron may be over-emphasized

Typically, the benefits of high dose iron include a rapid versus delayed rise in hemoglobin, reduced dosing of erythropoietin stimulating agents (ESA), and improved quality of life. The results of the PIVOTAL trial seemingly support this hypothesis by showing that proactive regimen resulted in lower administered doses of ESA compared to the reactive regimen. However, there may two sides to PIVOTAL. A closer inspection
of the reactive regimen demonstrates that patients in this group may have become iron deficient. Thus, a nuanced (skeptical) interpretation of the PIVOTAL results would be that iron deficiency is harmful relative to iron repletion.

Furthermore, in a retrospective cohort study of ESKD patients comparing the difference in hemoglobin between high dose versus low dose intravenous iron hemoglobin during 6 weeks of follow-up, the average absolute difference was only 0.15 g/dL between the two approaches. In the same study, the difference in erythropoietin dosing between the two iron dosing groups varied by time: at week 2 of follow-up, there was no difference in erythropoietin dose; at week 3, there was a modest difference; and by week 6 there was approximately a 1000 unit per week difference in average erythropoietin dose for the high dose compared to the low dose intravenous iron group. It is not clear whether either the absolute hemoglobin difference or ESA dose between groups receiving high dose and low dose intravenous iron is clinically meaningful.

Data for quality of life outcomes are even less clear than for hemoglobin or erythropoietin. In a retrospective cohort study of high dose versus low dose intravenous iron among ESKD patients, there was no improvement in overall quality of life measures as assessed by the Kidney Disease Quality Of Life survey for the group. However, among a subset of patients with low hemoglobin, less than 11 g/dL at baseline, high dose intravenous iron was associated with improved mental health scores compared to low dose intravenous iron while there was no difference in reported physical scores, or symptom scores.

Reason #4

_The risks of intravenous iron are not fully quantified_

PIVOTAL has shed light on the potential risks of intravenous iron. The trial found no infectious risk from associated with proactive dosing compared to reactive dosing. Proactive dosing demonstrated a cardiovascular benefit with respect to heart failure—consistent with studies from a non-ESKD population, individuals with chronic heart failure. However, there remains uncertainty because of current practice patterns, especially in the United States.

As previously stated, proactive dosing does not approximate high dose intravenous iron used in the United States. Therefore, there are no trial data for the risk
of high dose intravenous iron used for many patients with ESKD. While acknowledging that randomized control trials are not equivalent to cohort studies, there is remarkable consistency of the estimated risk of infection and cardiovascular associated with high dose intravenous iron across multiple epidemiologic studies in a recent meta-analysis\textsuperscript{10}. In fact, the marked heterogeneity of the studies makes the reported aggregate estimate potentially problematic. Furthermore, the studies with risk estimates whose 95% confidence intervals cross the null may have been underpowered.

Also, the risks of high dose intravenous iron remain undefined among certain subgroups of the ESKD population. These groups include individuals with active infections, hemodialysis catheters, and concomitant liver disease such as hepatitis B or C virus co-infection, nonalcoholic fatty disease, or cirrhosis. Should these individuals receive high dose intravenous iron? Out of an abundance of caution, low dose intravenous iron therapy may be the safe choice for them. Finally, we are only beginning to learn about the interaction of intravenous iron with an important marker bone and mineral disease, fibroblast growth factor 23 (FGF-23). Currently, the known intravenous iron preparations vary with respect to their ability to cleave and transcribe FGF-23. In current practice, we lack the ability to identify patients who may be harmed from rising FGF-23 values after intravenous iron administration.

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Author Contributions:

Abhijit Kshirsagar: Conceptualization; Writing - original draft; Writing - review and editing

Xiaojuan Li: Validation; Writing - review and editing

References

1. Sargent JA, Acchiardo SR: Iron requirements in hemodialysis. Blood Purif 22: 112-123, 2004
2. DOPPS Practice Monitor, Anemia Chapter. Available at
   https://www.dopps.org/DPM. Accessed on November 28, 2020.

3. Beshara S, Lundqvist H, Sundin J, et al: Pharmacokientics and red cell utilization of iron (III) hydroxide-sucrose complex in anemic patients: a study using positron emission tomography. *Br J Haemotol* 104: 296-302, 1999

4. Ferrari P, Kulkarni H, Dheda S, Betti S, Harrison C, St. Pierre TG, Olynyk JK: Serum iron markers are inadequate for guiding iron repletion in chronic kidney disease. *Clin J Am Soc Nephrol* 6: 77-83, 2011

5. Winterbourn CC: Toxicity of iron and hydrogen peroxide: the Fenton reaction. *Toxicol Lett* 82-83: 969-974, 1995

6. Macdougall IC, White C, Anker SD, et al: Intravenous iron in patients undergoing maintenance hemodialysis. *N Engl J Med* 380: 447-458, 2019

7. Kshirsagar AV, Li X. Long-term risks of intravenous iron in End-Stage Renal Disease patients. *Adv Chronic Kidney Dis* 26: 292-297, 2019

8. Kshirsagar AV, Freburger JK, Ellis AR, Wang L, Winkelmayer WC, Brookhart MA: Comparative effectiveness of intravenous iron in US dialysis patients. *Am J Med* 126: 541.e1-541.e14, 2013

9. Freburger JK, Ellis AR, Wang L, Butler AM, Kshirsagar AV, Winkelmayer WC, Brookhart MA: Comparative effectiveness of iron and erythropoiesis-stimulating agent dosing on health-related quality of life in patients receiving hemodialysis. *Am J Kidney Dis* 67:271-282, 2016

10. Hougen I, Collister D, Bourrier M, et al: Safety of intravenous iron in dialysis: a systematic review and meta-analysis. *Clin J Am Soc Nephrol* 13: 457-467, 2018