

A Randomized Controlled Trial of Intravenous or Oral Iron for Posttransplant Anemia in Kidney Transplantation

BACKGROUND:

- Posttransplant anemia is a common problem after kidney transplantation and has been associated with poor graft outcome and increased cardiovascular risks.
- Posttransplant anemia can occur any time after the transplant and can be from a number of different causes including: blood loss from the surgery, iron deficiency, immunosuppression, infection, or inflammation.
- Oral iron products are usually prescribed, but are not always optimal due to gastrointestinal intolerance and concerns regarding the decreased absorption of concomitant immunosuppressant medications.

OBJECTIVE

- To compare the time resolution of anemia in the postoperative period in kidney transplant patients between a single dose of IV iron and PO iron therapy

METHODS

- **Design:** Parallel, open label, randomized, active control trial
- **Inclusion criteria:** Patients must be undergoing living- donor or deceased-donor kidney transplant surgery, be 18 years of age or older, and able to give written informed consent
- **Exclusion criteria:** Iron overloaded (transferritin saturation >50% or ferritin >800 mcg/L); pregnant, lactating or of child-bearing potential and not using reliable contraception; have a history of psychological illness or a condition thought to interfere with the ability to understand or comply with the study requirements; previous intolerance of IV or PO iron
- **Primary outcome measure:** Posttransplant hemoglobin (Hb) concentration with the primary endpoint being the time to Hb \geq 11g/dL
- **Secondary outcome measures:** Presence of gastrointestinal symptoms (onset of nausea, vomiting, abdominal cramping, and diarrhea), infusion related reactions for patients in the IV iron group (self-limiting flushing, sweating, chills, myalgias, arthralgias, bronchospasm, or chest pain occurring during the time of infusion), acute rejection episodes, infectious episodes, and blood transfusion or erythropoietin stimulating agent (ESA) administration
- 102 participants, 51 in each group, were randomized to receive either 2 ferrous sulfate slow release tablets daily (equivalent of 210mg of elemental iron daily) on the fifth post-op day and continue until Hb \geq 11g/dL or a single 500mg IV infusion of iron polymaltose on the fourth post-op day
- To achieve 90% power ($\alpha=0.05$), a minimum of 48 patients in each group would have to be followed for up to 3 months to detect a halving of the time to correction of Hb levels to more than or equal to 110g/L in the IV iron-treated patients; P values were considered significant if < 0.05
- Data handling method was a modified intent-to-treat

RESULTS

- None of the patients were lost to follow-up; of the 102 randomized patients only 50 patients in the IV group and 48 in the PO group were included in the analysis due to 1 patient in the IV group and 3 patients in the PO group failing to develop anemia (Hb \leq 11g/dL)
- **Primary outcome measure:** There was no significant difference in the time to resolution of anemia when comparing IV with PO iron. The median times to resolution of anemia were 12 days in the IV group versus 21 days in the PO group (hazards ratio 1.22; 95% CI 0.82-1.83; P=0.32)
- **Secondary outcome measures:** There were no differences in the number of adverse events between the groups including infections (10 IV vs. 12 PO; P=0.62) and acute rejection (4 IV vs. 3 PO; P=0.68). There were numerically fewer patients in the IV group requiring transfusions (5 vs. 9) or suffering gastrointestinal side-effects (3 vs. 6) compared with the PO group, although neither of these results were statistically different (P=0.24 and 0.29, respectively). Also, erythropoietin requirements and graft functions at 1,2, and 3 months were not significantly different between the two groups.

- **Author's conclusion:** IV iron is not superior to PO iron for the resolution of early posttransplant anemia. For patients with previous intolerance of, or poor response to PO iron supplements or where gastrointestinal side-effects are concerning, a single dose of IV iron is a reasonable alternative to continuous PO iron supplementation during the postkidney transplant period.

STRENGTHS

- Randomized, active control trial
- IV and PO iron products are both widely available

LIMITATIONS

- Open-label design
- Effect size was too large
- Study was not powered to detect a difference in the secondary outcomes
- Iron polymaltose is a product of Australia, making it difficult to extrapolate the results to the iron products that are available in the US
- 57% of the patients were already considered iron replete
- Other causes of anemia were not considered such as blood loss, donor age, history of transplants, and use of other medications such as ACE inhibitors or ARBs
- Small one time dose of IV iron
- Reporting of gastrointestinal events was subjective
- Indication for the use of blood transfusions could be at the clinician's discretion

CONCLUSION

- Use of IV iron for the resolution of posttransplant anemia is just as effective as the use of oral iron, with much less of a risk for the gastrointestinal events and medication interactions that are associated with the oral formulations. In this study, the time to resolution was not statistically significant, however the use of IV iron did result in a median time to Hb of >11g/dL that was 9 days faster than seen with oral iron. The decision to use IV iron should be determined on a case by case basis taking into consideration factors such as poor response to oral iron in the past, likelihood of patient compliance, cost, IV access, and if iron deficiency is actually an issue or if supplementation is what is needed.
- Further study areas should include:
 - More robust sample size
 - Higher doses of IV iron
 - Comparisons between the different IV formulations

Reference: Mudge D, et al. A randomized controlled trial of intravenous or oral iron for posttransplant anemia in kidney transplantation. *Transplantation*. 2012;93:822-826.

Prepared by: Samantha J Martin, PharmD. Candidate