Reviewer’s report

Title: Protocol and baseline data for a Prospective open-label explorative randomized single centre comparative study to determine the effects of various intravenous iron preparations on markers of oxidative stress and kidney injury in chronic kidney disease (CKD). (IRON-CKD)

Version: 0 Date: 14 Nov 2018

Reviewer: Aala Jaberi

Reviewer's report:

In this manuscript, the authors propose a prospective open-label explorative randomized single-center comparative study to determine the effects of various intravenous iron preparation on markers of oxidative stress, inflammation and kidney injury in chronic kidney disease. Secondary outcomes include examining the haematic profiles and haemoglobin concentration, as well as, arterial stiffness and "quality of life".

It is feasible that the outcome of the study could inform on future clinical management for the patient cohort described herein. Moreover, the secondary outcome could help clarify the clinical implications of iron metabolism ultimately improving patient quality of life. However, there are several major and minor revision that should be considered.

Major Revisions:

1) The sample size is very small. Given the variability of F2-Isoprostanes and MDA measured by immunoassays in healthy population (see meta-analysis: Redox Biology (2017), 12, 582-599), do the authors anticipate that 40 patients will be sufficient to achieve statistical significance in their study? If they are using descriptive statistics, what sort of conclusions are the authors expecting to draw if variation is high and F2-IsoPs and MDA readings do not correlate? Perhaps a larger number needs to be recruited to make the study more impactful. It is also unclear whether the authors will use urine or plasma to measure F2-IsoPs.

2) The race of the patients is unclear. At least one study has found a significant correlation between MDA levels and race, as well as sex (see: American Journal of Epidemiology (2002), 156(3), p274-285). How will the authors control for these confounding factors?

3) Diabetes has shown in previous studies involving hemodialysis patients to have a higher propensity for lipid peroxidation during parenteral iron infusion. More than a quarter of the patients are diagnosed with DM. This can be a confounding element or independent
risk factor for inflammation. How will the authors address this (and other) confounding elements?

4) Only one of the newer, third generation iron formulations is evaluated in the study. These newer iron formulations have been determined to be safer and with less acute side effects. Given the advantages of the newer formulations, the authors need should clarify why they have chosen to evaluate only one of these formulations. Is it related to cost? Availability?

Minor Revisions:

1) The etiology of anemia specifically Iron deficiency anemia (IDA) is in some cases attributed to malnutrition. As such nutritional status should be included in the baseline characteristics in the form of serum albumin or pre-albumin.

2) Evaluation of the immediate consequence of hypophosphatemia maybe considered for each infusion group.

3) Which inflammatory markers will be examined? It is good that the authors mentioned that NGAL is also increased during inflammation. But it is unclear how will the authors distinguish between NGAL caused by inflammation and related to acute kidney injury in CKD patients which may have low chronic inflammation. Also recent studies has shown an increase in NGAL levels associated with iron stores in CKD patients with anemia.

4) Line 144 - no reference for the "specific levels" of the NGAL that are related to inflammation versus AKI.

5) It appears that majority of patients fall in the CKD stage IV where they may be at higher risk of developing AKI, given that CKD itself is a state of low chronic inflammation. As the authors hope to determine the impact of IV iron solutions on markers of AKI this patient cohort may present a problem.

6) Drugs that patient use including Proton pump inhibitors should be mentioned.
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