Dear Editor,

I am thankful to the reviewer for the very constructive comments and suggestions. The revised version of the manuscript is attached according to the reviewer's suggestions, with the revised/added contents highlighted with yellow color. The text is edited by a professional and a native English-speaking expert, and the language certificate is attached.

Reviewer #1

Dear Reviewer,

Thank You for Your valuable comments and extremely useful suggestions. Here are point-by-point responses to each of the specific comments.

The authors did a brief report about parenteral iron administration which was not widespread used nowadays. But as the new generation intravenous iron products were approved for pediatric patients, several reports have documented the safety and efficacy of parenteral iron. However, there are still some problems clinicians concern, which the authors need to address in the manuscript:

1. The authors should compare the bioavailability between oral iron products and intravenous iron products. The paragraph is added: There are insufficient data on the pharmacokinetics and pharmacodynamics of different iron preparations in the pediatric population. Repeated administration of iron sucrose, the most frequently used intravenous iron preparation in children, was effective in raising hemoglobin concentrations to normal in all children with IDA within 31-42 days after the first infusion. Administration of a single dose of intravenous ferric carboxymaltose in children unresponsive to oral iron therapy showed a complete hematological response in 49% of patients with IDA and 85% of all patients reached the target ferritin level within 12 weeks post-treatment. Likewise, dose-related increases in ferritin and transferrin saturation and clinically meaningful increases in mean hemoglobin concentration were observed from baseline to 35 days after a single intravenous dose of ferric carboxymaltose in children with IDA. These pharmacokinetic studies provide useful information regarding the optimal dosing regimen and potential adverse events, but more detailed investigation is required to better understand and predict the bioavailability of iron preparations.

2.Higher cost and limited medical resources actually are the main factors limiting the use of intravenous iron products. The authors should provide more data about pharmacoeconomics. The paragraph is added: Oral iron therapy with standard ferric salts is by far the lowest cost option and is readily available, but often of limited efficacy, with frequent gastrointestinal side effects and poor adherence. Conversely, intravenous iron formulations are associated with significant cost, yet have been previously shown to replenish hemoglobin levels more effectively than oral iron. Older-generation intravenous iron products have lower prices than newer-generation products. However, the latter may be associated with a reduction in total cost of care, mainly due to the lower number of venipunctures, better adherence, lower cumulative chance of infusion reactions or

extravasations, and increased convenience for physicians and patients. For all these reasons, physicians should consider the underlying disorder, the therapy goal, the response to prior therapy, patient tolerance and adherence, the cost, and the ease of access to the treating center when deciding on which formulation to use.

3. On the risk of iron overload, and the potential proinflammatory effect, are there any index for clinicians to monitor those side effects? The paragraph is added: High oral iron doses or rapid iron release from intravenous formulations can saturate the iron transport system, resulting in oxidative stress, with adverse clinical and subclinical consequences. A common concern is that intravenous iron may promote or exacerbate inflammation in anemic patients by triggering macrophage activation. While some studies have shown a transient increase in the circulating inflammatory cytokines IL-6, TNFα, CCL2 and INFγ, others observed no effect on the inflammatory markers IL 6 and IL 10. Further research is required to better understand the pro-oxidant and proinflammatory potential of intravenous iron.

Following seven references are added (5/7 published from 2022-2024): Korczowski B, et al. 2023; Geisser P, et al. 2011; Kumar A, et al. 2022; Lucas S, et al. 2024; Polson MK, et al. 2023; Vinchi F, et al. 2019; and Kassianides X, et al. 2022.

I truly hope that the revision is done well and thank again for the review.

Jelena Roganovic, MD, PhD, Prof.