

Post-Operative Intravenous Iron Therapy Mitigates Prolonged Systemic Inflammation Following Orthopedic Trauma

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INTRODUCTION: Acute blood loss in orthopedic trauma contributes substantially to anemia, which is associated with worse surgical outcomes including increased hospital length of stay, cardiovascular complications, and death^{1,2}. Moreover, independent of trauma, anemia has been associated with elevated inflammation as the disruption of iron homeostasis dysregulates inflammatory cytokine production^{3,4}. Because prolonged acute inflammation after trauma is detrimental to bone healing, resolving perioperative iron deficiency may improve excessive inflammation and thus overall bone regeneration. Recent work from our group found that perioperative anemia was prevalent in 93% of patients with lower extremity orthopedic trauma⁵. Of this cohort, 70% of patients with anemia did not reach the stringent blood transfusion thresholds (hemoglobin < 7 g/dL) while 95% had sustained derangement in their iron axes⁵. Given the significant number of patients with less severe anemia (hemoglobin 7-12 g/dL) in the setting of functional iron deficiency are left with no standard treatment, our group began a randomized, controlled clinical trial utilizing intravenous iron therapy (IVIT)⁶ to evaluate an alternative treatment. We hypothesized that traumatic injury would dysregulate iron homeostasis for extended periods after injury resulting in prolonged systemic inflammation. Further, the resulting perioperative iron deficiency could be treated in the acute post-op period via IVIT to mitigate iron deficiency and reduce excessive inflammation following traumatic orthopedic injury.

METHODS: Patients admitted to Oregon Health and Science University's level 1 trauma center after traumatic injury requiring operative fracture management were prospectively evaluated and enrolled into a double blind RCT (April 2022—August 2023, conducted under IRB#22441)⁶. Eligible subjects included adult patients with either a lower extremity or pelvis fracture and hemoglobin of 7-11 g/dL. Patients were randomized to either a single dose infusion of 1000 mg low molecular weight iron dextran (n = 13) or normal saline placebo (n = 11) post-operatively. Patients with post-operative surgical complications were excluded from the present analysis. Complete blood count (CBC) and plasma were obtained from blood samples collected 0-, 2-, 4-, 6-, and 12-weeks post-op. To quantify systemic inflammation, 36 inflammatory cytokines related to the inflammatory and immune response were quantified via multiplex assays run on the Luminex 200 system. Reference ranges were used to interpret laboratory values as normal and are visualized in green on graphs (**Fig. 1**). Two-way ANOVA with Tukey post-hoc testing was used to test for significance (p < 0.05) between timepoints and groups.

RESULTS: The age of patients enrolled into the iron (n = 13) and placebo (n = 11) arms were 59 ± 20 and 50 ± 20, respectively, with no statistical difference in BMI at 32.5 ± 17.0 and 34.6 ± 13.9, respectively. No differences in hemoglobin, hematocrit, white blood cell count (WBC), or platelet count were found between IVIT and placebo treatment at any timepoint (**Fig 1**). Hemoglobin and hematocrit measurements significantly increased at each timepoint after injury (p < 0.0001) and were returned to normal ranges within 4-weeks post-op for all patients (**Fig 1A**). While WBCs were significantly higher 0-weeks post-op for both the IVIT and placebo groups compared to all other timepoints (p < 0.01), all measurements are within the normal reference range (**Fig. 1B**). Platelet count significantly increased 2-weeks post-op (p < 0.0001), peaking outside of the normal range, and returned to within the normal range at all other timepoints (**Fig 1C**). When normalized to each patients' baseline (post-op week 0) cytokine levels, IVIT treatment significantly attenuated the increase in key inflammatory plasma cytokines after trauma, including Eotaxin, MCP-1, and TNFα (**Fig 2A**). Elevated inflammation was sustained 12-weeks post-op in untreated patients compared to IVIT treatment (**Fig 2B**, n = 9).

DISCUSSION: Prolonged, elevated inflammation out to 12-weeks post-op was evident in patients treated with placebo compared to IVIT. However, because hemoglobin and hematocrit levels appear to normalize within 4 weeks post-op independent of IVIT treatment, further research is needed to understand the impact of IVIT and its link to systemic inflammation. Regardless, IVIT attenuated increases in systemic inflammation—commonly associated with poor healing outcomes—thus supporting further investigation into IVIT for trauma care.

SIGNIFICANCE/CLINICAL RELEVANCE: While this clinical trial is ongoing and further investigation is pending, these preliminary results suggest a single, post-operative dose of IVIT is a feasible treatment to potentially mitigate chronic inflammation in trauma patients. Thus, IVIT may bridge the gap for the large prevalence of patients with peri-operative anemia that are above the threshold for blood transfusions but still experience the negative consequences of functional iron deficiency.

REFERENCES: Manuscripts are listed as PMID, abstracts with full citation: ¹32583812; ²31149970; ³36816471; ⁴36654387; ⁵Peterson DF *et al.* "High Rates of Body Iron Store Derangements and Anemia Above the Transfusion Threshold Observed in Patients Following Orthopaedic Trauma" *ORS* 2022; ⁶36944463

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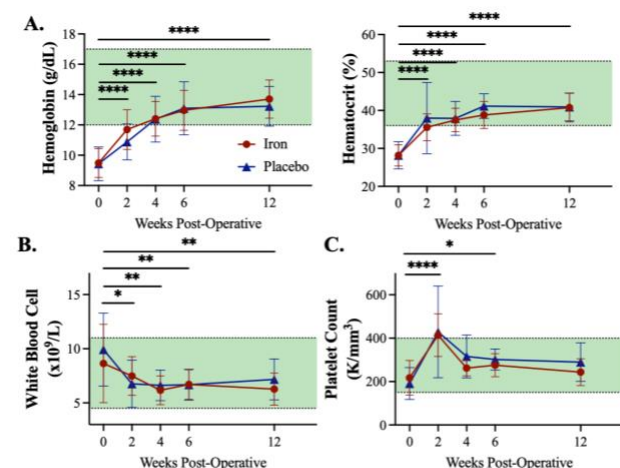


Figure 1: Longitudinal measurements of (A) circulating iron, (B) white blood cell, and (C) platelet counts in patients treated with IVIT or placebo post-trauma. The standard reference range is indicated in green for each measurement (green). All significance tests were performed between baseline (0-weeks post-op) and each longitudinal timepoint. No significant differences were found between IVIT and placebo treatments at any timepoint. * P < 0.05; ** P < 0.01; *** P < 0.001; **** P < 0.0001

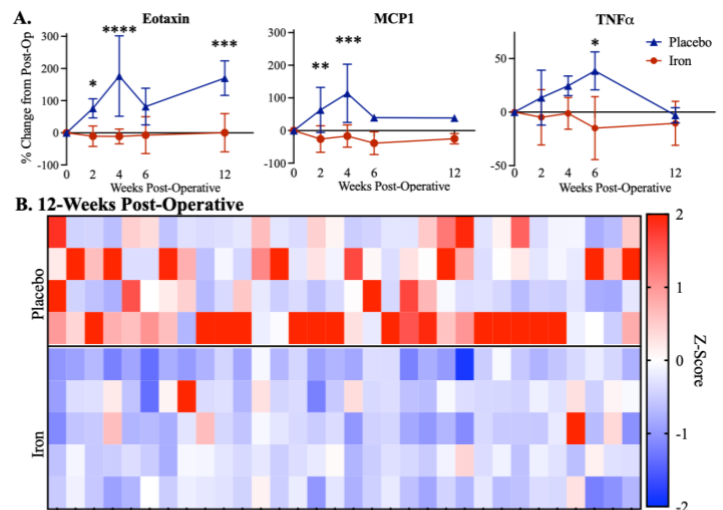


Figure 2: IVIT treatment after trauma reduces systemic inflammation. (A) Biomarkers are presented as a percent change as they are normalized to each patients' baseline (0-weeks post-op) cytokine levels. (B) Heat map represents each biomarker normalized via z-score. * P < 0.05; ** P < 0.01; *** P < 0.001; **** P < 0.0001