Intravenous Iron Therapy Alters the Inflammatory Cascade Following Orthopaedic Trauma: A Pilot Randomized Controlled Trial

*Victoria R. Duke; **Danielle Peterson, MD**; Natasha S. McKibben, MD; Catherine E. T. Hutchison, MD; Chih- Jen Yang, MD; Colby Curtis, BS; Karalynn Lancaster, BS; Talia Trapalis, BS; Dongseok Choi, PhD; Joseph Shatzel; Graham J. Dekeyser, MD; Darin M Friess, MD; Martin A. Schreiber; Joseph Aslan; Zachary M. Working, MD; Karina Nakayama, PhD; Nick Willett*

Purpose: Acute blood loss anemia is highly prevalent in patients following lower extremity orthopaedic trauma; many patients stay above the transfusion threshold and remain largely untreated. Sustained anemia and iron deficiency can lead to elevated inflammation. We hypothesize intravenous iron therapy (IVIT) would restore iron levels and mitigate elevated inflammation.

Methods: This double-blind randomized controlled trial evaluated IVIT for treatment of anemia after orthopaedic trauma (Level I academic, 2022-2024; patients with operative lower extremity or pelvis fracture; hemoglobin 7-11 g/dL postoperatively). Subjects were 1:1 randomized: single-dose low-molecular-weight iron dextran (1000 mg, n = 18) or saline placebo (n = 18). Peripheral blood was drawn 0/2/4/6/12 weeks postoperatively and processed into plasma for multiplex inflammatory protein quantification. Timewise linear models estimated fold changes with false discovery rate (FDR)-adjusted P values.

Results: Patients treated with IVIT had 11, 16, 6, and 16 total significantly differentially expressed inflammatory proteins (FDR-adjusted P<0.05) 0/2/4/6/12 weeks postoperatively, respectively (Fig. 1A). At 2 weeks postoperative, 8 proteins were elevated in IVIT patients, while a different set of 13 proteins had increased levels 4, 6, and 12 weeks postoperative (Fig. 1A). Importantly, key pro-inflammatory cytokines (tumor necrosis factor [TNF]α, interleukin [IL]-6, and IL-1β) were significantly decreased postoperatively (Fig. 1B).

Conclusion: Pilot data suggest IVIT alters the overall systemic inflammatory cascade and attenuates inflammation in key inflammatory cytokines after orthopaedic trauma.

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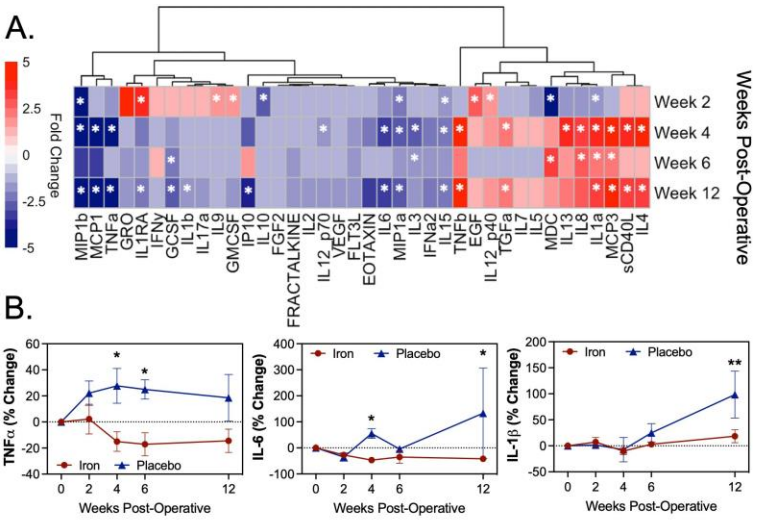

Figure 1: Longitudinal differentially expressed inflammatory proteins in patients treated with intravenous iron compared to saline placebo. (A) Clustered heat map of the fold change of plasma protein expression in patients receiving IVIT compared to placebo. Significant differences are determined through a linear mixed model; FDR adjusted p-value < 0.05 are denoted with a white *. **(B)** Percent change of longitudinal protein expression of key inflammatory proteins, normalized to each patients' baseline (0-weeks post-op). Significant differences are determined by a linear mixed model; FDR adjusted p-value: * < 0.05, ** p < 0.01.