

Increased Prothrombotic Plasma Cytokine Levels Are Associated with Hypercoagulability Based on Thrombelastography in Patients Requiring Hip Fracture Surgery

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Disclosures: Prism Schneider (5-Johnson & Johnson, Smith & Nephew; 8-Canadian Journal of Surgery, Osteoporosis Canada), Paul Duffy (3B-Stryker, DePuy Synthes; 4-Tactile Orthopaedics), Ryan Martin (1-Tactile Orthopaedics; 4-Tactile Orthopaedics)

INTRODUCTION: The risk for venous thromboembolism (VTE) after hip fracture surgery (HFS) remains high, at 2.5%, despite the use of post-operative thromboprophylaxis. The pathophysiology for VTE remains poorly understood in this high-risk patient population. Though there is increasing evidence supporting the interplay between hypercoagulability and inflammation during clot formation, this relationship has yet to be studied in the hip fracture population. Cytokines are inflammatory mediators that can promote thrombus formation (interleukin (IL)-6, IL-9, IL-17A) or resolution (IL-4, IL-8, IL-10). IL-6 promotes a hypercoagulable state through upregulation of tissue factor and PAI-1, and both IL-6 and IL-8 promote procoagulant activity by increasing platelet aggregation.

Thrombelastography (TEG) is a whole-blood assay which provides a comprehensive analysis of hemostasis from clot initiation to fibrinolysis and can identify orthopaedic trauma patients at increased risk for in-hospital VTE. This study aimed to use serial TEG analysis and inflammatory cytokine analysis to describe the relationship between pro- and anti-inflammatory cytokines and hypercoagulability. We hypothesized that the pro-thrombotic cytokines would be elevated during states of hypercoagulability.

METHODS: This is a single centre prospective cohort study of consecutive patients requiring HFS. Following institutional research ethics board approval, eligible participants who provided informed or surrogate consent underwent serial blood draws until 6-week follow-up, at times determined *a priori*. Serial whole blood analyses were performed using a TEG6s hemostasis analyzer (Haemonetics Corp) to quantify hypercoagulability and the MESO QuickPlex SQ 120MM (Meso Scale Diagnostics) was used for plasma cytokine analysis. Patients used pharmacological thromboprophylaxis for 28 days post-operatively. Incidence of VTE (proximal deep vein thrombosis [DVT] or pulmonary embolism [PE]) was monitored throughout the study. Maximal amplitude (MA, a measure of clot strength) was evaluated using TEG, with hypercoagulability defined as MA greater than or equal to 65mm. Mann-Whitney U test were used to compare cytokine levels in two groups (hypercoagulable MA=65mm or greater and non-hypercoagulable MA<65). For cytokine level comparisons, a Benjamini-Hochberg procedure is used to control for false discovery rate. Spearman correlations were calculated between MA and cytokine levels.

RESULTS: In total, 99 patients were included in this analysis with a median age of 79 years (IQR 71-86.25) and with 63% being female. There were two symptomatic VTE events (2%) in this cohort, with both participants having elevated MA at the time of their VTE diagnosis (VTE 1: MA=66.1 on POD 2 and VTE 2: MA=66.7 on POD 3). Our results demonstrated that IL-17A and interleukin-2 receptor antagonist (IL-2Ra) are statistically significantly elevated at admission and on post-operative day (POD) 1 in patients who were hypercoagulable based on TEG analysis. Additionally, IL-22 was significantly elevated on POD3 in the hypercoagulable group. The highest correlation between MA from TEG analysis and cytokine level is for IL-2Ra at 0.26, followed by IL-9 at 0.25.

DISCUSSION: The inflammatory cytokine IL-17A has been linked to thrombus formation, and these results demonstrated significantly elevated early IL-17A levels, supporting that hypercoagulability may be, in part, inflammatory-mediated. This novel data also suggests that there is weak monotonic relationship between IL-2Ra and IL-9 and hypercoagulability, based on serial TEG analysis. The heterogeneity of comorbidities and surgical treatment type (i.e., fixation vs. arthroplasty) may contribute to the variability in inflammatory responses. However, this study identified trends in post-operative hypercoagulability and quantified inflammatory cytokine levels in patients requiring HFS for the first time.

SIGNIFICANCE/CLINICAL RELEVANCE: This large prospective cohort of patients requiring HFS who underwent serial TEG analysis and inflammatory cytokine analysis supports that further research is warranted to investigate inflammatory-mediated hypercoagulability, especially with respect to IL-17A and IL-2Ra. This data may help inform future novel therapeutic targets for VTE risk reduction.

ACKNOWLEDGEMENTS: Orthopaedic Trauma Research Team at the Foothills Medical Centre and our participating patients.

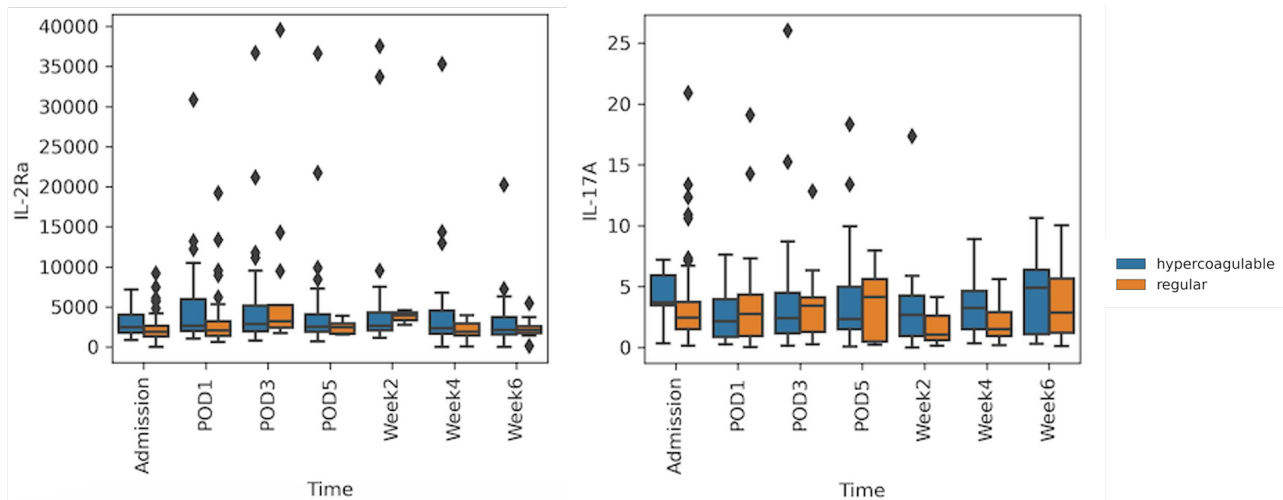


Figure 1: Serial inflammatory cytokine levels compared between patients requiring hip fracture surgery (HFS), who were hypercoagulable (maximal amplitude [MA] of 65mm or greater) post-operatively compared with those who were not (regular), supporting that elevated interleukin-2 receptor antagonist (IL-2Ra) and IL-17A levels may contribute to post-operative hypercoagulability.