Tocilizumab mitigates hypercoagulability after out-of-hospital cardiac arrest – results from a randomized controlled trial (IMICA)

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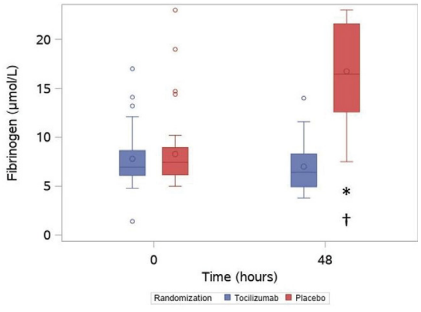
Background: Systemic inflammation constitutes a key element of the post cardiac arrest syndrome (PCAS) which affects initially comatose resuscitated cardiac arrest patients. We have recently shown that treatment with tocilizumab, an IL-6 receptor antagonist, reduces systemic inflammation and myocardial injury after out-of-hospital cardiac arrest (OHCA). Inflammation and coagulation are interconnected, and changes in coagulation often accompany inflammatory states.

Purpose: To investigate if conventional coagulation parameters or a viscoelastic hemostatic assay differ in patients treated with tocilizumab compared to placebo.

Methods: Eighty comatose OHCA patients were randomized 1:1 in a double-blinded placebo-controlled trial to a single infusion of tocilizumab or placebo in addition to standard of care including targeted temperature management. Trial registration: Clinicaltrials.gov NCT03863015. Endpoints were plasma fibrinogen, platelet count, and Thrombelastography (TEG) variables. TEG analysis was performed utilizing whole blood in a citrated kaolin assay with heparinase (to neutralize any unfractionated or low molecular weight heparin that had been administered), and the following variables were analyzed: reaction time (R), angle, maximum amplitude (MA), and lysis at 30 minutes (Ly30) which represents clot initiation, propagation, strength and dissolution respectively. Data reported as median (Q1; Q3), statistical analysis performed by constrained linear mixed models, and a $p<0.05$ was considered statistically significant.

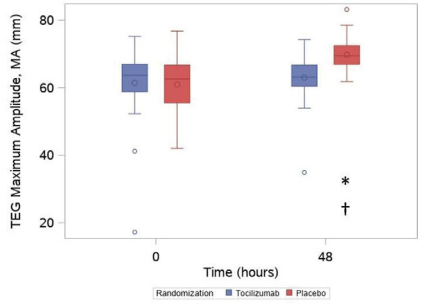
Results: Admission median levels of the investigated coagulation parameters were within normal levels for both the tocilizumab and placebo group. At 48 hours, for the placebo group, fibrinogen levels (figure 1) had risen to supra-normal levels, TEG angle had increased from 64 (10; 67) till 72 (69; 74), and TEG MA (figure 2) had increased to the hypercoagulable range (all $p<0.05$), while for the tocilizumab group fibrinogen levels and TEG MA remained within normal values. Both groups had a significant fall in platelet count from admission till 48h [placebo: from 252 109/L (208; 282) till 151 (126; 189); tocilizumab from 217 (183; 260) till 152 (127; 183)], with no group differences. Also for both groups there was significant shortening of the TEG R time [placebo: from 8 min (6; 10) till 6 (6; 8); tocilizumab from 8 (6; 9) till 7 (6; 8)], again with no difference between groups. Ly30 did not change over time or differ between groups.

Conclusion: Treatment with tocilizumab following resuscitated OHCA aids in maintaining a normo-coagulable state, whereas placebo patients developed supra-normal fibrinogen levels and a hypercoagulable TEG clot strength.



Normal range 5.3 – 10.3 µmol/L
*, p<0.05 for tocilizumab vs. placebo
†, p<0.05 vs. hour 0

Figure 1. Fibrinogen



Normal range 51 – 69 mm
*, p<0.05 for tocilizumab vs. placebo
†, p<0.05 vs. hour 0

Figure 2. Thrombelastography MA