Complement System Targets and Models

Development of a Clinically Relevant Trauma Model for Evaluation of Complement Inhibitors

Development of complement inhibitors for trauma management requires appropriate animal models that recapitulate the immunological and pathophysiological processes experienced by humans. To address this need, researchers at U.S. Army Institute of Surgical Research (USAISR; Fort Sam Houston, TX) have developed a clinically relevant rat model of blast injury and hemorrhagic shock.

In their model, rats were exposed to 116 kPa overpressure then immediately experienced a 50 percent blood loss. After a 30-minute period they were provided fluid resuscitation and observed. Levels of complement factors were measured in blood drawn at each step of the injury model.

The combined injury protocol resulted in multiple organ damage, hemorrhagic shock, a high mortality rate (70 percent), metabolic acidosis, and hyperkalemia. Levels of C1q, C3, and plasminogen were significantly lower immediately after shock through 3 hours of follow up than at baseline, but differences were no longer significant after 24 hours (Figures 1, 2, and 3). This combined trauma model mimics clinical immune physiology and complementopathy and will provide a valuable platform for testing the efficacy of immune modulators, such as complement inhibitors, following trauma.

This effort was supported by USAMRMC and is strategically aligned with CCCRP. The award is managed by DHA.

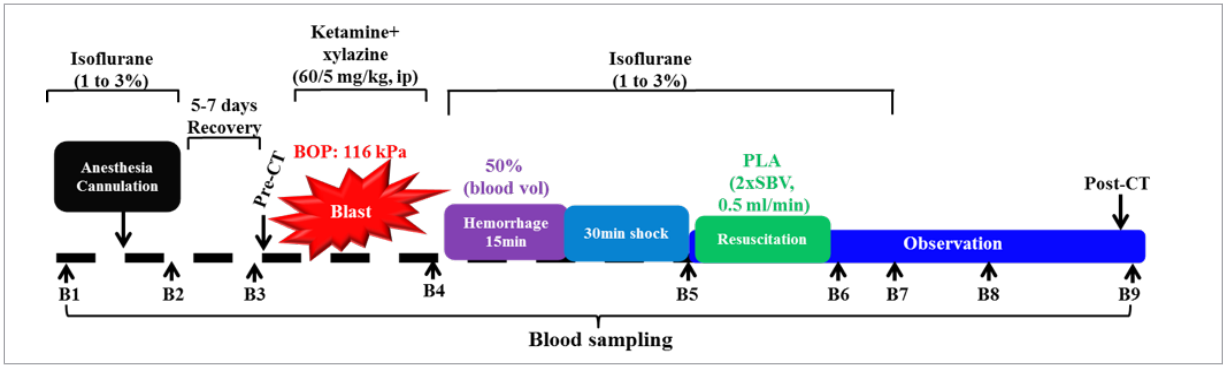

FIGURE 1: Experimental design and timeline.

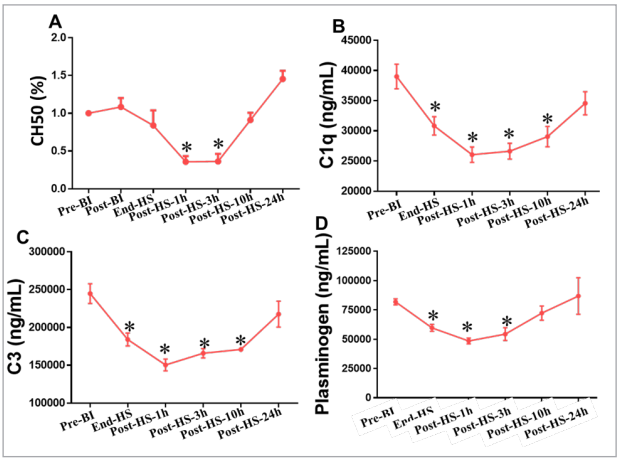

FIGURE 2: Complement activation/consumption in rats after blast injury and hemorrhagic shock. The hemolysis activity (CH50, A), complement components of C1q (B), C3 (C), plasminogen (D) were determined by ELISA. The data are expressed as mean ± SEM, and comparison was performed by two-tailed unpaired t test with Welch's correction: * $p<0.05$, individual time points vs. Pre-BI.

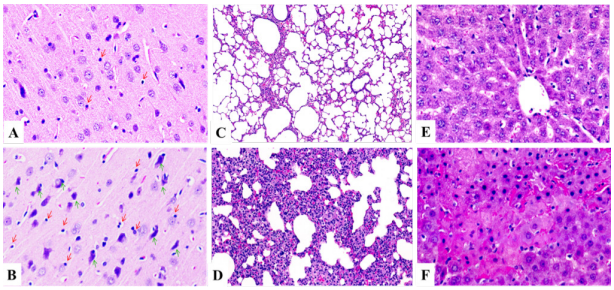

FIGURE 3: Multiple organ damage after blast injury and hemorrhagic shock in rats. Tissue histological alterations were evaluated in H&E-stained paraffin slide. Compared to the sham (A), injury in gray layer of cerebral cortex showed neuronal apoptosis and microglial infiltration (B). The representative photomicrographs were shown with the lung damage characterized by inflammatory infiltration, septal thickening, and hemorrhage (D) when compared with the sham (C). C, the liver damage characterized by hepatic nuclear condensation, coagulation necrosis and inflammatory infiltration (F) compared with the sham (E).