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Re: The whole is greater than the sum of its parts: hemostatic Profiles of whole blood variants

Lucy Z. Kornblith, MD and Mitchell Jay Cohen, MD

Department of Surgery, San Francisco General Hospital and the University of California, San Francisco; San Francisco, California

Lucy Z. Kornblith: lucy.kornblith@ucsfmedctr.org; Mitchell Jay Cohen: mcohen@sfghsurg.ucsf.edu

We respectfully appreciate the AUVA's interest in our work and their specific concerns over the prolonged standard coagulation measures and out of range ROTEM measurements in our study. We strongly disagree, however, that there are any compelling methodological issues, and additionally disagree that it is difficult to explain these findings in the banked products compared to healthy volunteer blood. Unfortunately the editorial claims seem to be based on incorrect assumptions regarding methodology and results, which we seek to remedy here. To clarify, our regional blood collection center colleagues collected the donated whole blood in a collection bag prefilled with 70 mL of anticoagulant, primarily citrate phosphate dextrose per standard protocol. The clinical standard acceptable volume of whole blood for collection is 450mL-550mL with added 70mL of anticoagulant (which results in variable 13-16% anticoagulant). The whole blood units provided to us were either slightly overweight or underweight and therefore had a mean anticoagulant of 17%, only 1% above the clinical standard. Each whole blood unit was split into four satellite bags without anticoagulant (designed specifically to avoid excess dilution and to standardize surface contact) and therefore retained their anticoagulant concentration after the split. For the reconstituted whole blood components, the red blood cells, platelets, and plasma (whole blood derived) all had an anticoagulant concentration of 15%. Therefore, the mean concentration of anticoagulant across all the products we analyzed was 15-17%, making it appropriate to compare coagulation measurements between these banked products.

Next, all samples were run in standard citrated tubes. The total citrate concentration in our samples most certainly inactivated some of the calcium, but we believe that the suggestion that all available calcium needed for coagulation was inactivated is incorrect. There is more than sufficient calcium to recalcify these blood samples ensuring appropriate assay. In fact, suggestion that inadequate recalcification occurred is contradicted by our ROTEM data demonstrating intact coagulation with overall clot strength measured by ROTEM within normal range for modified whole blood variants (all of which had approximately 17% anticoagulant). Further evidence is provided by Mann et al, who demonstrated that alterations of coagulation with citrate anticoagulants found on thrombogram and thromboelastograms are not reversible by calcium replacement, and that the effects of citrate may alter the natural dynamics of tissue factor-induced blood coagulation separate from chelation of calcium (1). Lastly and most importantly, we feel the discussion of dilution and recalcification is misguided, as the absolute coagulation measurements of the banked products were not the critical finding of our study, but rather the comparison between the

products, which demonstrated superiority of 1:1:1 reconstituted whole blood to 2:1:1 and of modified whole blood to 1:1:1 reconstituted whole blood. These comparisons are the pivotal results, which provide important insight into characterization of blood products and their use in resuscitation.