Discussion of 2021-1731

FIBRINOGEN IS AN ESSENTIAL EARLY COMPONENT IN THE MANAGEMENT OF TRAUMA INDUCED COAGULOPATHY

**DR ANDREW C BERNARD** (Lexington, KY): I would like to congratulate the groups from Colorado and now Miami for another significant contribution to the trauma and coagulation literature and thank them for their continued investigation into one of the most fundamentally important clinical problems facing us in trauma and surgery, that of hemorrhage and coagulopathy.

Since the last session of the Southern Surgical Association, US troops have been mostly evacuated from Afghanistan, where the War on Terror began 20 years ago. It was during that broad and sustained military offensive that we witnessed a new paradigm in surgical research–the description of trauma‑induced coagulopathy. It was early in that conflict that investigation in the theater of war and at home laid the foundation for the current standard of care in trauma resuscitation we termed "massive transfusion protocols," "trauma exsanguination protocols," or "balance resuscitation". Whatever you call it in your center, this resuscitation strategy is plasma and platelet forward, and we can all agree on that. But what remains unclear today is the optimal timing and formulation of fibrinogen replacement. Dr Meizoso and colleagues have analyzed tier 1 trauma activations over 7 years from a prospectively collected database at the Ernest Moore Shock Trauma Center and shown that more severe injury, more shock, and more coagulopathy all predicted depleted fibrinogen on arrival. Cryoprecipitate transfusion was associated with higher fibrinogen levels; the optimal fibrinogen restoration strategy was a combination of cryoprecipitate and plasma given early (within 4 hours) and, most importantly, if fibrinogen was corrected by 24 hours, mortality was dramatically reduced. This study is relatively small, and thus unable to completely adjudicate some secondary endpoints. It is a retrospective analysis of prospectively collected data. But all that considered, these findings are important and lend further support to the role of early, empiric fibrinogen replacement with the goal of reducing mortality related to hemorrhage.

The criticism of early high plasma ratio resuscitation studies was that the findings could be related to survival bias. Can the same criticism be leveled toward the mortality reduction in the fibrinogen replacement group in your study?

The Prospective, Observational, Multicenter, Major Trauma Transfusion (PROMMT) study taught us that we must reach high plasma-to-red-blood-cell (RBC) ratios, and we must hit those targets early. What was the fresh frozen plasma (FFP):RBC ratio in your population? In patients whose ratio approached 1:1, is the impact of fibrinogen replacement attenuated?

Should we be using cryoprecipitate, or should we be using fibrinogen concentrate, and what would be the dose?

Who should receive early empiric fibrinogen? Can you provide us with the equivalent of Bryan Cotton's Assessment of Blood Consumption (ABC) score for fibrinogen replacement?

Does your analysis provide any further evidentiary support to whole blood coagulation monitoring as superior to standard plasma‑based coagulation studies?

Lastly, what is the impact of fibrin degradation products on the sensitivity of your fibrinogen analyses, and could they have somehow reduced the sensitivity of your analysis?

**DR JUAN C DUCHESNE** (New Orleans, LA): In their study, the authors sought to analyze in a prospective fashion the true incidence of low fibrinogen levels in patients who received massive transfusion of more than 10 units RBC over the first 6 hours. Their working hypothesis was that low fibrinogen level is common at hospital arrival and is an integral component of trauma‑induced coagulopathy, which carries a high mortality rate. From a cohort of 476 patients, they found an incidence of 15% low fibrinogen level upon admission. The authors concluded that low fibrinogen level can predict the need for activation of massive transfusion protocols and, not surprisingly, they found that cryoprecipitate transfusion results in the most expeditious correction, with the recommendation to incorporate earlier infusion of cryoprecipitate as part of massive transfusion protocols.

Based on your single-center analysis, the incidence of low fibrinogen level was not very high. With 15%, incidence but with a high mortality rate, it seems like we need to center more work on our efforts to predict or diagnose low fibrinogen level in a timely fashion. Is your team looking at specific point-of-care analysis or prediction models that our first responders or the emergency room could use to promptly diagnose and manage low fibrinogen level patients? Or should we aim to start replacing it in patients with a positive ABC score and systolic blood pressure less than 70 mmHg on the field?

As we know, the European guidelines stress that correction of low fibrinogen levels with fibrinogen concentrate or cryoprecipitate is a priority in managing trauma‑induced coagulopathy with incorporation of fibrinogen on their massive transfusion protocols. But in the US, we are still looking for evidence on where exactly to incorporate its use. Are you proposing giving freeze‑dried fibrinogen concentrate or cryoprecipitate to all patients who receive 1 unit of blood or get a massive transfusion protocol activation? And if so, how early we should administer it?

Were you able to analyze the impact of tranexamic acid in combination with early cryoprecipitate in patients with trauma‑induced coagulopathy? In your time-to-correction curves analysis, it seems like FFP and cryoprecipitate were the best way to correct low fibrinogen level in a timely manner. It makes me wonder what would happen if you added tranexamic acid to that equation, by halting fibrinolysis.

Based on this important contribution, it seems that our massive transfusion protocol guidelines should center more and more on prompt recognition and management, with early infusion of this vital clotting stabilizer with fibrinogen concentrate/FFP and potentially tranexamic acid. I would like to urge authors to continue reviewing multi‑institutional prospective analyses to determine where exactly in the process we need to incorporate its infusion. In most US massive transfusion protocols, its use is random and not standardized, with usual incorporation late after 10 units of transfusion.

**DR BRYAN A COTTON** (Houston, TX): Your center carried out a randomized control trial, showing the superiority of rapid thromboelastography (TEG)‑guided resuscitation, improved survival, and lower blood use using rapid TEG, unlike conventional studies, which used international normalized ratio (INR), platelet count, and fibrinogen. Why look at absolute fibrinogen count for a hypofibrinogenemic state? Why not look at the functional fibrinogen?

Your conclusion was that we should use more cryoprecipitate in massive transfusion. In 2012, we eliminated cryoprecipitate from our massive transfusion protocol as an automatic. It is still available as needed or on request. When we performed the same analysis, we had less than 1% hypofibrinogenemia based on a fibrinogen count of <150 mg/dL. The solution, I think, is in your methods when you look at the ratios. You are administering what a lot of people would say is an inferior ratio combination, and I know Dr Moore would disagree with that, but you are using 2:1. You are running a plasma fibrinogen deficit by using 2:1. If you administered more, I would expect you to see more of what we and others are seeing, which is a less than 1% hypofibrinogenemic state. So, maybe reconsider a 1:1 ratio, or a whole blood‑based resuscitation, because plasma has a decent amount of fibrinogen.

**DR ROBERT MAXWELL** (Chattanooga, TN): Do you had a recommendation on how to incorporate the cryoprecipitate into your massive transfusion protocol? We have been giving it for a while, and we used to give it starting with the second round. We found a lot of patients with lethal injuries were dying during the second round, so that cryoprecipitate was often wasted. As a result, we decided to start it during the third round of our massive transfusion protocol instead.

**DR JONATHAN P MEIZOSO** (Miami, FL): To address Dr Bernard's questions first, the issue of survival bias is present with any of these resuscitation-type studies. Part of what we did in the time analyses and the survival analyses was to attempt to censor that by including it into the model. I think that that is something that needs to be considered when interpreting these results. In terms of the ratios, we did not look at the ratios of FFP and RBC before writing the manuscript; what patients received vs what we started giving them with our empiric transfusion ratios, so I will go back and look at that. In terms of fibrinogen vs cryoprecipitate, which one is the better supplementation? Unfortunately, I do not have any magic answers for that. There are several studies currently underway in Europe trying to answer that question for trauma patients. I think that currently, in the US, the go‑to is cryoprecipitate, because we do not have the indication for fibrinogen use in trauma patients. I think we need the equivalent of an ABC score. That may be the next extension of this project, to see if there is something that we can create to help us predict who is going to be hypofibrinogenemic on arrival. In terms of whole blood monitoring and which is going to be the superior test, our group performed a randomized controlled trial in Denver several years ago showing that whole blood testing with TEG was superior to conventional coagulation tests for several outcomes. We did not include some of the analyses we performed because we are still teasing them out, but we looked at the correlation between things like the maximal amplitude (MA) and the angle on TEG and how that correlates to Clauss fibrinogen. We found very modest correlation between angle and MA, but interestingly, MA performed just as well as angle in our studies. Traditionally, you think of angle for fibrinogen and MA for platelets, to simplify the interpretation of these viscoelastic results, but I think it is more complex than that, and our preliminary data suggests that as well.

I think that degradation products have decreased the sensitivity of our studies, and I think that is why we need to perform a more sophisticated analysis with viscoelastic testing.

Regarding Dr Duchesne's questions, I think that we need a multicenter study, even if it is a prospective observational study at first, to understand this problem a little bit better. I think that looking at things like functional fibrinogen, which is available in TEG, is great. It depends on what the centers have available, however, and many centers are not currently able to do that, so they must rely on things like the traditional Clauss fibrinogen levels. So, I think our results are more relatable to some centers that do not have those things.

In terms of when to give cryoprecipitate, unfortunately, I do not have a definitive answer to that either, although it seems like 4 hours is the number our data would support. Earlier studies out of Denver would support that cryoprecipitate should be given after patients have received about 5 units of red blood cells.