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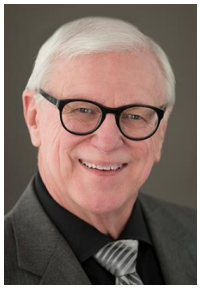
Transcript – Coag Conversation

Trauma-induced Coagulopathy
Mechanisms, Management and the Laboratory's Contribution
Part 3: "Trauma-induced Coagulopathy
The Laboratory's Role in Care

Featuring:



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Transcript of the Conversation—Part 3:

Mr. Fritsma: Hello and welcome to Coag Conversations, an educational series sponsored by Biomedica Diagnostics of Windsor, NS, Canada.

Our topic for this series is Trauma-induced Coagulopathy: Mechanisms Management and the Laboratory's Contribution to Care.

I'm George Fritsma, faculty for the University of Alabama at Birmingham, School of Medicine, Division of Laboratory Medicine and Proprietor of the Fritsma Factor, Your Interactive Hemostasis Resource, where we exchange current information on coagulation mechanisms, clinical observations and the role of the laboratory in diagnosis and management of disorders.

It's my pleasure to introduce our guest, Dr. Maureane Hoffman. Dr. Hoffman's research focuses on the role of cellular features in controlling hemostasis and thrombosis. Her collaboration with Drs. Mac Monroe and Harold Roberts led to the development of an in vitro, cell-based model that mimics many aspects of hemostasis in vivo. Their work has clarified why the deficiency of factor VIII or factor IX in hemophilia leads to such a severe bleeding tendency and how hemostatic agents such as prothrombin complex concentrates and recombinant activated factor VII enhance thrombin generation.

Dr. Hoffman has clinical interests in component and pharmacologic therapies for bleeding disorders and laboratory monitoring of anticoagulants and transfusion therapy. Dr. Hoffman obtained her MD and PhD in pharmacology and toxicology from the University of Iowa. She completed residency training in anatomic and clinical pathology at Duke University in Durham, NC.

Dr. Hoffman's current position is as Professor of Pathology at Duke University and Director of the Transfusion Service and Core Laboratories at the affiliated Durham VA Medical Center. She has authored or co-authored over 200 journal articles and 15 book chapters, and has lectured extensively in the US and internationally on basic and clinical laboratory aspects of coagulation. She was recently honored with an Esteemed Career Award from the International Society on Thrombosis and Haemostasis.

We conclude our three-part series today as we discuss The Laboratory's Role in Trauma-induced Coagulopathy Care.

Mr. Fritsma: Dr. Huffman, last month we discussed the management of Trauma-induced Coagulopathy. What part does the laboratory play in delineating the TIC mechanism?

Dr. Hoffman: Well, I think that the laboratory doesn't actually delineate the TIC mechanism. What we do in the laboratory is let the clinicians know or provide additional information on the resuscitation effort really. So, when the patients arrive at the emergency department, very often they are in the process of or about to undergo a massive transfusion.

They very often already have a coagulopathy and, as part of the damage repair and resuscitation, they're going to receive primarily blood products, but also possibly pharmacologic agents. So, the laboratory provides information on what blood products are most appropriate, whether the things that you can measure readily with blood samples are getting better or not. And then, if transfusion therapy really is not correcting the issues, can sometimes guide the decision to move to pharmacologic therapies such as prothrombin complex concentrates, fibrinogen concentrates or recombinant activated factor VII.

Mr. Fritsma: This is an aside, but are we using a fair amount of the activated factor VII these days, or has the use of that fallen off? I know back in the time of the Afghanistan and Iraqi wars the medics are all carrying NovoSeven with them in their pockets and giving it to everybody. Is it still being used that extensively?

Dr. Hoffman: No. In caring for injured individuals in the field, you pretty much have to have a very clear protocol. So like with the TXA [tranexamic acid], I personally think that's quite appropriate to give to just about everybody that looks like they stand a chance of having massive bleeding and requiring massive transfusion. That's really not the way you want to use recombinant FVIIa. So recombinant FVIIa benefits those individuals who are destined to undergo massive transfusion.

So, if someone only is going to require two or three or four units of red cells, they really are not the person that should get recombinant FVIIa because there absolutely is a thrombotic risk. Maybe not as definitely, not as much with younger individuals. So, in a military setting, the young, healthy guys are less likely to have a thrombotic complication than the old folks with vascular disease and perhaps pre-existing thrombotic issues. But nonetheless, if you give that to somebody that really doesn't need massive transfusion, that's not bleeding massively, it's all downside and no upside.

And so that's not a treatment that you can easily protocolize and say, OK, everybody gets this. In my opinion, and I think I'm not unusual in this regard, but in my opinion, I think the people that need recombinant FVIIa are the people that fail transfusion therapy. So what you want to do is to use transfusion therapy as best you can and identify as early as you can those individuals that are simply not getting enough benefit from transfusion therapy.

So for example, if somebody's getting all the platelets that you've got available to give them, and that seems to be the main issue with their hemostatic function but, their TEG or ROTEM, that is viscoelastic testing parameters, are not getting any better, their coagulopathic bleeding is not getting any better.

And you're pretty much giving them maximal transfusion therapy. That's the person that should be considered to move on to getting PCC's [prothrombin complex concentrates] or recombinant FVIIa.

And not just anybody that comes through the door and has used a couple of units of red cells. You want to make sure that if there's downside, you've chosen the person that has a lot of upside to giving them recombinant FVIIa. But you want to make that decision as early as you reasonably can, because the sooner you take that step, the more likely they are to benefit from it. That is my opinion.

Mr. Fritsma: Well, that's very helpful because I know back in, you know, around 2007, 2008, everyone was using the NovoSeven at that time. But, I knew that had fallen into disfavor because of the thrombotic risk.

Dr. Hoffman: One of the problems here is that it is very hard to run a clinical trial to look at recombinant FVIIa; recombinant activated FVII, in the way it should be used in the real world. Because if you're going to run a clinical trial, you have to have clear inclusion criteria and in order to accumulate enough patients to really do a clinical trial that probably has to be something like they've suffered trauma of the kind you define, that your study defines, and have bled more than so many or have required transfusion of more than so many units. Or, you don't wait until they've already received a massive transfusion to consider them for entering into your trial.

So, there are quite a few people that aren't destined to truly receive massive transfusion that end up getting the FVIIa. And by and large, they don't benefit. And the people that have received a massive transfusion are the ones more likely to benefit, but they are a smaller proportion of your trauma patients than people that need any transfusion at all.

And so, when you look at the data collected on everybody that shows up in your emergency department and needs at least 2 units of red cells, most of those people are not going to need FVIIa and so the right trials have never been done and so, I would not say that FVIIa is too dangerous to use. It's too dangerous to use if you give it to the people that don't need it.

And so it's not that you can't do it, you can't either do a clinical trial that way, nor can you use it for real in a military setting when you have to use clinical judgment at a fairly high level, to decide who gets it; who doesn't get it.

Mr. Fritsma: It might also be difficult that you don't really have a good lab assay to tell you what the effectiveness is of the FVIIa.

Dr. Hoffman: Absolutely. So, the effectiveness has to be monitored clinically, and sometimes it's dramatic. So coagulopathic bleeding means that blood is oozing from all cut surfaces. You know, the microvascular bleeding is the hallmark of coagulopathy.

If you've got a hole in your aorta, you'll bleed no matter what your hemostatic state is with that, with that oozing everywhere is typical of coagulopathy. And in some proportion of those patients when you give them the FVIIa, the field dries up. And but there is no lab test to tell you whether it works or not. If you can't see the bleeding and you give somebody recombinant FVIIa and you don't know whether you gave them the right dose or not or whether it was effective or not.

And so that's another problem. But again, if you're talking military, they're not going to do many lab tests no matter what. They're going to manage the acute things that can be managed and get that person transported out to a medical treatment facility.

So FVIIa is not the right drug for the medic in the field because they have to give it to everybody.

Mr. Fritsma: The issue of testing brings me to asking, in the past, it seems as though the patient's condition was based on the PT and the PTT, and you see studies where if the PT is twice of normal or the PTT is twice normal, you know that's when the patient is the sickest. Is that the best way to do it?

Dr. Hoffman: Well, probably not, but we don't know what the best way is. So, the way patients in some of the initial studies, with trauma-induced coagulopathy were identified was by noting what PT was when they arrived in the emergency department. So, they're the people that very rapidly after trauma had a prolonged PT, were

the ones that had a coagulopathy. And so, these are people that hadn't gotten a lot of crystalloid or anything like that to dilute the procoagulants, and yet they had a prolonged PT, so that was a bad sign. That doesn't tell us that much about mechanism, but we don't really have any great tests that do tell us about mechanism. As we discussed in the first of these conversations, there are many things that contribute to the coagulopathy in trauma.

Some of them are things that are very difficult to assay no matter what, like endothelial health. But even if you have an assay for one of those things, there are probably half a dozen things that contribute to the NET, I guess you would call it phenotype and the patient to the bleeding phenotype.

And so, at the moment, we don't really have a great test for that because we don't know enough about the relevant mechanisms. And it may be that trauma patients could be categorized into groups with different prevailing mechanisms. And then you could categorize the patient, then test for that mechanism for the health or dysfunction of that mechanism.

But at the moment that's not available. So that's part of the problem. Now from a treatment point of view, our lab tests aren't that bad. So, if the PT or PTT is prolonged, there's a problem with the plasma procoagulants because that's what they assay.

They don't reflect anything with platelets. They don't reflect anything with the anticoagulants. And so a prolonged PT or PTT says we should give plasma. Now we don't do platelet function testing in the lab. We can do a platelet count and platelet function is reflected in the TEG and ROTEM or more common viscoelastic tests. So you can get an idea of whether the individual needs platelets.

Certainly, if the platelet count is 10,000, they need platelets. If it's harder to say that someone with a pretty acceptable platelet count has platelet dysfunction.

Because in my opinion the viscoelastic tests are not very specific about distinguishing whether there's a platelet problem or whether there's a lack of, particularly fibrinogen. But we can get some idea of whether platelets might be needed and we can get some idea of whether fibrinogen might be needed because we can look at the TEG or ROTEM and we can also do a direct measurement of fibrinogen levels. So I think our lab tests are not half bad for the resuscitation part.

For distinguishing mechanism, no, we're not there yet.

Mr. Fritsma: I guess you're not going to test cytokines or endothelial cells?

Dr. Hoffman: Maybe someday there might, you know. Might be the right—you know, maybe someday when the person rolls through the door, there'd be a quick test for, you know, this package of pro inflammatory cytokines. And you can say, oh, that patient's really going have trouble down the road. This mechanism is likely operating, but we're nowhere near that at this point.

Mr. Fritsma: So besides thinking about just the traditional lab test, besides pro time and PTT, Do you use any of the others routinely at the start, like thrombin time, fibrinogen? Do you get pH, blood gases or D-dimer?

Dr. Hoffman: Sure. So, we encourage fibrinogen levels early. It bears mentioning that both the patient's temperature, hypothermia and the patient's blood pH, acidosis dramatically affect coagulation directly. They're not just bad signs that the patient is sick, which they are. But the enzymes and the coagulation process depend on having the right environment to function optimally, and so when it's colder, they turn over less rapidly. And when the pH is lower, it dramatically reduces their activity. In fact, our coagulation enzymes are more closely related structurally to chymotrypsin, which likes an alkaline pH. So, dropping the pH from 7.4 to 7.2 reduces the activity of any one of the coagulation proteases by about half. So, those things that are not reflected in our lab test and have an absolutely dramatic effect on the hemostatic capacity.

Mr. Fritsma: Does D-dimer do anything for you in trauma?

Dr. Hoffman: I don't think at the acute stage that that's very helpful. Because it should be elevated because the organism should be trying to clot and thrombin should be generated. Fibrin should be formed and so you're going to get some D-dimer.

Now later on, the course of the D-dimer level can be helpful to you, but in the in the acute phase that really doesn't matter to how you're going to try to resuscitate or manage the patient.

Mr. Fritsma: Ever since COVID, it seems like you can't pass a hospital without having a D-dimer done on you.

Dr. Hoffman: That might be true.

Mr. Fritsma: Yeah, and I get inquiries from people who have a chronic, elevated, isolated D-dimer and quite high and it stays high like that and nobody seems to know what that means. And I like to explain to them just that we know the D-dimer test is very sensitive and it's positive in any form of inflammation. And that never quite answers people's questions. And you know, as a lab scientist, I don't go any farther than that.

Dr. Hoffman: Yeah, it's not very specific, but before COVID anyway, we used to say that we ought to look at that person for occult cancer. Because a lot of those folks have low grade compensated DIC and the thrombotic tendency on that basis.

Mr. Fritsma: So, but now let's go back to viscoelastometry, because I know we've had the TEG since, 1948? And it always seemed like more art than science. But we're using it more and more. Not just the TEG, but the ROTEM, the Quantra. And so what's your experience with those instruments?

Dr. Hoffman: Well, so the TEG. The forerunner of our modern TEG was developed because we really didn't have any tests at all at that time. And looking at whole blood clotting was a reasonable way to go. And even now the structural integrity of the clot, as an endpoint, is very appealing. The problem is that especially the TEG, the performance characteristics of the TEG were determined by the materials available at the time.

And so, there's a pin in a cup that turns, and it's on a wire, and the mechanical properties of that whole set-up determine the sensitivity of the system to clot structural integrity. And that might not be optimal, but that evolved because you had those materials.

And subsequent generations of tests have kind of been calibrated to the old-fashioned TEG, say oh, this has performance characteristics similar to the TEG the FDA should approve it.

And that's good because we have experience with the TEG. But, for example, in hemophilia the TEG or ROTEM is not the right answer. If you are going to try to monitor, say bypassing agent therapy with recombinant FVIIa or activated PCCs in a patient with hemophilia, neither the TEG nor the ROTEM are useful without a whole lot of manipulation of the data; processing of the data.

And so you would think that being able to form a structurally stable clot would be a good way to predict what patient would respond to what hemophilia patient would respond to a bypassing agent, but they just don't work for that purpose. And I consider that to be a matter of how they're calibrated, what they're calibrated to do and not deliberately calibrated. But the way they evolved. And so they do tell us things about clot stability but, like with any model system; so, a lab test, a functional lab test, is a model system. They have their limitations.

And one of those limitations is what do you use as an activator, for example. And then what do you use as a detection method? Well, not all activators are appropriate for all questions you're going to ask. And so I think you just have to be familiar with the performance characteristics of your model system and it does appear for patients with trauma, for example, some intraoperative bleeding situations that the TEG or ROTEM does reflect what's happening clinically with the patient.

So we use it, but we don't use it for hemophilia much, because it doesn't really reflect clinical reality. When we give something like recombinant activated factor FVII to any of these patients, it affects the assay way more than

it affects the patient. So low doses of recombinant FVIIa make big changes in your TEG or ROTEM or your PT; bigger than they make in the in the bleeding patient. And so, as you alluded to, we don't have a test, a good test to monitor the effects of FVIIa, because those lab tests were not developed for that purpose.

I sort of got off on a little bit of a of a tangent with respect to managing trauma-induced coagulopathy, but at least many aspects of coagulopathic bleeding, whether perioperatively or post trauma, do seem to be reflected reasonably well in the viscoelastic tests (VET). And because they seem to do something useful for us, their use has been increasing.

Mr. Fritsma: There's an effort for VET to be used in selecting components for caring for trauma-induced coagulopathy, you need plasma, platelets, red cells and so on? And also in a different application, for monitoring heparin as well. Is that pretty effective? It's nice that it's fast. You know right at the bedside and immediate, is it effective ?

Dr. Hoffman: Yeah. So, I believe it sounds like it's an article of faith-based on my experience and some data the TEG or ROTEM or any of these viscoelastic tests will tell you whether something is wrong with the blood part of hemostasis. They are not that specific about telling you what's wrong.

And they also can tell you whether things are getting better or getting worse. So, if you have somebody who's bleeding and your viscoelastic test looks perfectly normal, you either have a problem that's not reflected well, you have a problem, it's not reflected in the test.

So, for example, maybe there's a surgical problem that there's a hole that needs to be filled patched. Or, maybe the patient is hypothermic and or acidotic and that doesn't show up in our lab tests because the reagents are buffered, and they're performed at a standard temperature. But if the assay is abnormal and you say, well, I think this maybe means you need platelets, you give platelets and it gets better. Well, fine. You can monitor your platelet transfusion that way. But as far as pegging the components, you give very precisely to parameters of the TEG or ROTEM, I just don't think it's that specific.

Mr. Fritsma: One of the questions is we tend to want to use TEG or ROTEM to track hyper versus hypo fibrinolysis. And is that a possibility?

Dr. Hoffman: It is a possibility. We don't have much that we can do in the clinical laboratory to monitor fibrinolysis. TEG or ROTEM will reflect systemic fibrinolysis. The problem is that most fibrinolysis is local, not systemic. And so when you form a fibrin clot, tissue plasminogen activator, or, UPA will associate with the clot as will plasminogen which gets activated to plasmin right there in the vicinity of the fibrin clot.

And if you get much plasmin formed at a site of injury but don't establish hemostasis very effectively, then any further fibrin deposition that takes place is sort of going against the fibrinolytic environment that's already been established since plasmin has been activated in fibrinolysis.

That is not going to show up on the viscoelastic testing because it's a local phenomenon. Fibrinolysis is supposed to be local. Now, it's very obvious if systemic fibrinolysis is going on and that will show up on your viscoelastic tests.

But not all fibrinolysis will show up on your viscoelastic test. So, somebody might benefit from TXA, from tranexamic acid, even though their TEG or ROTEM doesn't show systemic fibrinolysis.

Mr. Fritsma: Well, that's interesting. And then I think this will be my last question. How will the lab help you to figure out whether you are still in a hemorrhagic [state], or if the patient has transitioned to later stage thrombophilia?

Dr. Hoffman And again, that's that is a very difficult thing and I don't think you can depend on the lab test. That is a setting where in some people, their D-dimer has been high because they've suffered a lot of tissue injury. They've made a lot of fibrin clot, but it seems it's stabilized or maybe even started to drop. And you certainly see

this postoperatively. If it then starts to rise, that suggests that thrombin generation has increased fibrin formation, and might at least get your attention. It could be something like sepsis, so it could be infection or it could be thrombosis. And those are things to at least keep in mind if you've been tracking the D-dimer and it starts up.

But there's not a whole lot that the clinical lab can do that really tells you is this person currently developing thrombosis.

Mr. Fritsma: So there's more work to be done.

Dr. Hoffman: There's a lot of work to be done, that's for sure.

Mr. Fritsma: OK. Well, thank you so much, Dr. Hoffman. This concludes our third and final conversation and we appreciate your expertise. We encourage participant questions and comments and there's a link on the BioMedica Diagnostics website for you to download a transcript of today's talk and forward your questions or comments.

Thanks again for listening and thanks to BioMedica Diagnostics for sponsoring Coag Conversations and thank you for your participation.

Questions or Comments? Please email to: Webinars@BioMedicaDiagnostics.com