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Emerging Data on Reversal and Repletion for Anticoagulated Patients with ICH: The Neurocritical Care Perspective

Announcer:
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Dr. Kreitzer:
Well, thank you all for coming out this morning. My name is Natalie Kreitzer. I am an Associate Professor of Emergency Medicine and Neurocritical Care, and then also am a member of the University of Cincinnati's Stroke Team. So I'm going to discuss Repletion and Reversal for Anticoagulated Patients with ICH: The Neurocritical Care Perspective, and specifically discuss warfarin reversal as we begin our journey of anticoagulation reversal.

So for those of you in this room, this is all review information. We know that intracerebral hemorrhage is a small minority overall of all types of strokes. However, it has a much higher mortality than ischemic stroke. And about 74% of patients are, in some capacity, functionally dependent still at 12 months. It's thought that the incidence of ICH is likely to double by the year 2050, and this is due to our aging population, as well as increased uses of anticoagulation.

Now the primary ICH is something that Dr. Patel will discuss and some surgical options that are available, but one of the biggest aspects that is crucial is trying to prevent secondary injury to the brain once the ICH has occurred. And a big mechanism of this is trying to reduce the chances of hematoma expansion.

Now you can see in these two slides, an example of hematoma expansion. This occurs in patients who are not anticoagulated at about a rate of about 33% of those patients, depending on which study that you're looking at, or different types of epidemiology databases. And it's typically defined as a 1/3 size increase in the volume of the hemorrhage. Now we also know that patients who experience hematoma expansion have a much worse outcome compared to patients who do not have hematoma expansion.

Now, when we type think about these types of patients when they come to us in the emergency department, oftentimes they show up with little to no information available. And for me, when I work in the emergency department, these patients, it's very hard to know what their last-seen-well time is. It can be hard to know what time they last took their medication, or even if they are on an anticoagulation medication. So for that reason, in any patient who has a diagnosed intracerebral hemorrhage, it's crucial to really understand what type of anticoagulation medication are they on, because now with different types, that dictates anticoagulation reversal, and when was that last dose that they took it? And then, when we think about the types of lab testing in those patients, of course, they're all going to require a CBC with platelet count, an INR, PTT, and then, depending on your institution, the potential for thromboelastography or platelet function assays.

Now, when we think about the types of patients broadly who may be reversed, compared to those who are not, at least starting out with the mindset of thinking that almost all patients should receive some type of reversal, and then working backwards from there to figure

out maybe who doesn't fall in those buckets, is a great way to think about this.

Some of the pitfalls are the idea of ultra-early prognostication. For ICH specifically, we know that outcomes may improve all the way out to 12 months after ICH. So that first day really does not give us the very best picture of how a patient may do long term. The second is waiting for a decline in their exam or waiting for a hemorrhage to get worse before providing reversal. At that point, you've really missed the opportunity to provide the best impact not reversing small hemorrhages, particularly those in the ultra-early time frame from their last-seen-well time and those patients who are anticoagulated. And some considerations to keep in mind are their times since their last DOAC. If it's been, for example, over 15 hours or 24 hours, they may not even require reversal. Or INR, in patients who are taking warfarin, it's possible they may not even be taking their medication. Age, comorbidities, location, size of hemorrhage, and then your own institutional guidelines and protocols that you may need to follow. And several of these are considerations will be discussed in the upcoming talks.

Now, when we think about the American Heart Association guidelines regarding warfarin, the AHA guidelines, they say that the INR is elevated because of a vitamin K antagonist, and those patients, of course, should have that warfarin or VKA withheld and receive therapy to replace those vitamin K-dependent factors to correct the INR and receive the IV vitamin K. We know this because these medications have been around for quite some time, and there's a lot more data, especially compared to the DOACs.

Now when it comes to warfarin reversal, or vitamin K antagonist reversal, PCCs may have fewer complications and correct the INR more rapidly than FFP.

Now when we think about a patient who is anticoagulated with warfarin, it's important to understand that time is critical for preserving the best outcomes in these patients. This was a study that was published in 2015, so it's a bit of an older study, and it was in patients who were taking warfarin, a large retrospective database from several institutions within Europe, and basically looked at the rates of hematoma expansion when patients were provided anticoagulation reversal as well as blood pressure control early compared to later. And what this study demonstrated that there is a significantly lower rate of hematoma enlargement in these subjects when they were reversed to an INR that was less than 1.3 and a systolic blood pressure of less than 160 within 4 hours of their last-seen-well time.

Now I mentioned the idea of PCCS and anticoagulation reversal and repletion; when we think about patients who are on vitamin K antagonists, we have two options for repletion: FFP and PCCs. FFP contains all of the factors that are needed for all of us. These are large volumes that we have to give to our patients, 10 to 15 cc/kg. It takes time to prepare. Patients are at risk of volume overload. Now, if we think about our trauma patients, that's kind of what we want, is that large amount of volume. But in our patients with ICH that's not really the case. With PCCs, you have factors – 4 factors and 3 factors, generally 4 factor, which is 2, 7, 9, and 10. Those are typically a faster reversal. Less volume needs to be infused, but it does come at an increased cost.

Well, I'm now going to ask the panelists if we have any questions about warfarin-associated ICH?

Dr. Gibler:
Dr. Steiner.

Dr. Steiner:
What to do?

Dr. Kreitzer:
The expert.

Dr. Gibler:
Just from a perspective that you see an evolving evolution away from vitamin K antagonists, but that's there's still an important part of practice. How do you all feel that this fits into your all's practice? And do you see things that, from our audience perspective, that would be helpful?

Dr. Steiner:
Yeah, as I'm saying to my colleagues, we should not forget to know how to use vitamin warfarin, or in our country it's phenprocumon, because there are still people who are on coumadins, and there are a couple of indications where these drugs are still given. So I can only say, don't forget about how to treat complications like intracranial hemorrhages and obviously everybody has paid attention to Natalie's nice presentation. And yes, that's the answer. The reason for the vitamin K, and that is important to remember, is that the half-life time, at least for in Germany, that's very important for phenprocumon, is 7 days. So when you jump in with prothrombin complex, where the factor with the longest half-life time is factor 10, which is about 7 hours or so somewhere, then you have the effect of the warfarin or of the phenprocumon coming back, and that's the reason why you need to add vitamin K. That's very important.

Dr. Gibler:

Yes. Adrian, you look ready to speak?

Dr. Parry-Jones:
I was just going to add in, we see it much less now, of course, as well, it's sort of 10 to 20% of anticoagulant-associated ICH. But one thing I remember about speeding up the pathway for this was that introducing point-of-care INR testing was really helpful, and sort of knocked about an hour off the time to treatment. So it sort of reminds me that we don't have that advantage now with DOACs, that we have a very quick, easy point-of-care test to know who's to treat and who not to treat. So it'll be interesting to see what we discuss about that in the future talks.

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