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Providing Optimal Care for the Anticoagulated Patient with Intracranial Hemorrhage in the Acute Care Setting: Does the Patient Need Reversal, Repletion, or Surgery?

Announcer:

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Dr. Gibler:

So, our first presentation, and you can read it here, is essentially providing optimal care for the anticoagulated patient: reversal, repletion, or surgery. Dr. Natalie Kreitzer is Associate Professor of Emergency Medicine Neurocritical Care, and a member of the UC Stroke Team from the University of Cincinnati. And I'm absolutely delighted to have Natalie here tonight. And she will give you that perspective from the neurointensivist, which I think you'll find very important. Natalie?

Dr. Kreitzer:

Well, thank you so much all for coming this evening. Thank you, Dr. Gibler. As he mentioned, I'm neurocritical care emergency medicine, I'm part of the UC Stroke Team. I'm going to provide some background about ICH, as well as reversal, repletion, and different neurosurgical indications, probably largely review for this particular audience, but a great background for what's to come with some of the other speakers.

So, we know that one of the, if not the biggest predictor of how a patient does with an intracerebral hemorrhage is going to be the initial size of that hemorrhage. And unfortunately, that's really not something that we can impact as much. That's largely going to be through preventative measures, largely before that ICH occurs. What we do hope to impact, however, is hematoma expansion. And I have this included on this slide. And we've certainly all seen this in practice before, unfortunately. And we know that a certain percentage of patients, whether they're anticoagulated or not, are going to have this hematoma expansion. We also know that this is an independent predictor of poor outcome, regardless of how much the hematoma expands, but certainly the larger it gets, the worse the patient is going to do in the long term.

Now, I do just briefly want to go through the coagulation cascade. I know it's everybody's most exciting slide to look at, so. But it's important when we're talking about the way the DOACs work and some of these vitamin K antagonists. So, here we have the coagulation cascade. We have, of course, all of our factors. When we think about those vitamin K antagonists, associative factors, those are going to be II, VII, IX, and X, those that are vitamin K dependent and created in the liver. Now, at least for me, throughout, you know, my medical school training, residency, and you know, at least the beginning of fellowship, that was the predominant anticoagulant that patients were on. And we all got very good at reversing those patients or repleting those factors. But then came along the DOACs. And those are direct inhibitors of factors in particular. So, for example, apixaban, rivaroxaban, down here, they're our anti-Xa factors. And so, you can see where those impact the thrombin, and ultimately, the fibrinogen turning into fibrin, which reduces the risk of that clot formation.

Now, when we think about the concepts of repletion and reversal, they're actually two separate ideas. So, reversal are going to be for those specific agents that are inhibitors of different factors in that clotting cascade. And those are going to be andexanet alfa for factor Xa inhibitors as well as idarucizumab, or Praxbind, for the direct thrombin inhibitors, or dabigatran. When we think about repletion, we're thinking about giving a patient who's low in factors 2, 7, 9, and 10, some of those factors back. So, that's going to be through FFP, which of course has all of the factors. But for ICH in particular, more so the 4-factor PCCs, Kcentra, because we do know that those work much faster at decreasing that INR.

And when we think about some of those repletion strategies I mentioned, the differences between FFP as well as PCC, just briefly. But to go into a little bit more detail about what we're looking at, the FFP includes all of those factors. Some of the disadvantages are those patients that require large volumes, there's a lot more time to prepare and administer, the risk of fluid overload, and transfusion reaction. So, it's great in our trauma patients in the emergency department who require those large-volume resuscitations, but not something that we want to utilize, for example, in a patient who is on warfarin with an intracerebral hemorrhage, and we want to quickly reverse them.

Now, PCCs are 4-factor, 3-factor most commonly are going to be the 4-factor 2, 7, 9, and 10, activated versus inactivated, and depending on different local protocols may be fixed or based on the INR and weight. This provides faster reversal as well as less volume, but does come with increased cost.

Now, to get a little bit more detail about what some of those reversal strategies look like, I've got a couple of publications, both from *New England Journal of Medicine*, looking at dabigatran reversal for idarucizumab, that direct thrombin inhibitor, as well as andexanet alfa. And this is ANNEXA-4 study specifically, looking at reversal of the factor Xa inhibitors. Now, dabigatran is a monoclonal antibody that binds – or I apologize – dabigatran is a monoclonal antibody that binds – idarucizumab binds to the dabigatran, and it is usually needed if the patient has had their last dose within the past 12 to 24 hours. And the lab to follow is going to be the PTT as well as the thrombin time, and that's typically a fixed dose of 5 grams. I personally have not seen a patient who is on dabigatran for several years, but this would be what the reversal agent is.

Now, andexanet alfa is a recombinant modified human decoy factor Xa protein. And that's used if - may be needed if the last dose is around 18 hours. That was what the ANNEXA-4 study employed, although ANNEXA-1 was 15 hours. Now, of course a lab to follow is that anti-Xa level, and for us in Cincinnati, it's just gotten to be a lab that we can actually get back in a reasonable timeframe, but I know that that's not the case everywhere. The dose is going to be a high dose or a low dose, and it is completely dependent on the Xa inhibitor dose that the patient is on, as well as the time that they took it. It's not weight based, it's not severity based.

Now, when we think about the types of patients with intracerebral hemorrhage who have some type of surgical indication. So, we've talked a little bit about what the medical management of reversal or repletion might look like. We can look at the 2022 guidelines from the American Heart Association, American Stroke Association, and look at what some of those options might be. And the ones I'll bring up are those minimally invasive options which still are 2a for mortality, 2b for functional outcomes. I'll talk about EVDs on the next slide. Supratentorial craniotomy is again 2b. I'll talk specifically about the craniotomy for the posterior fossa, or the SOC as we call it in the neurocritical care. And I do want to highlight that that is the only one that really has that AHA/ASA recommendation of 1, level of evidence B-NR, and this is largely because we know that without these SOCs, these patients would die. And then craniectomy lastly at 2b.

And then just going through some of those levels of evidence. When we look at IVH specifically, those patients that have that class 1 evidence are going to be those with spontaneous IVH who have obstructive hydrocephalus, require the external ventricular drain, and they'll see that mortality reduction as class 1 with the functional outcome benefit as class 2b. Now, sometimes that's combined with a thrombolytic to try to break down the clot in the ventricles or a neuroendoscopy.

Dr. Gibler:

So, if you have questions, please, you can submit them through the website. I wanted to open this up to our panel here and see if they have questions of Dr. Kreitzer. And I have something to start with; it's just from the standpoint of emergency physicians, individuals that see patients first with this, you're talking about a cerebellar hemorrhage as being what should be identified as a potential neurosurgical emergency. Is that correct or not, from your perspective?

Dr. Kreitzer:

Yes, absolutely. Yeah.

Dr. Gibler:

So, that's the one that should wave a red flag with, that's probably obvious for many of the people in the room, but as an emergency physician, that's something that we care deeply about. Any other thoughts here, Dr. Kreitzer?

Dr. Parry-Jones:

I was just wondering with patients on anticoagulants come in with an ICH, there's often quite a lot of uncertainty isn't there, about, I guess a number of things, but particularly when did they last take their anticoagulant? Did they take it? And the sometimes when the onset of the ICH is? So, I just wondered whether, you know, in your own practice how you manage that uncertainty? And what you would do in terms of reversing anticoagulation? It's a difficult one.

Dr. Kreitzer:

Yeah, that's a tricky thing to sometimes figure out. So, the question was thinking about the onset of the ICH or the last seen well time in these patients, as well as whether they're on an anticoagulant, and how to figure out what their dose is and what time that they last took it. So, unfortunately, that can sometimes be pretty challenging and be a little bit of a treasure hunt in trying to figure out some of those pieces of information. So, in our emergency department, we've got social workers, we've got pharmacists, and they're often quite good at trying to get a hold of family members and figuring out what times they typically take their medications, and with the pharmacists to see if they're actually filling their prescription. And, again, as I mentioned before, the anti-Xa level, but I do understand that that's not available everywhere yet.

Dr. Gibler:

And then that probably, you know, for most hospitals in the country, the anti-factor Xa levels are not available, right, in a real-time basis that you can do?

Dr. Kreitzer:

That's correct.

Dr. Gibler:

So, you would have to do it more to, I think, Dr. Parry-Jones's point is you have to make that decision clinically based on the timing of the last dose, right?

Dr. Kreitzer:

Correct. That, and they may not always be specifically calibrated to the anti-Xa that the patient has taken.

Dr. Gibler:

Oh, yeah. We have an audience question. What is the recommendation for timing with neuro symptoms for cerebellar bleed as per the AHA/ASA? And I think what they're trying to get at is what sort of - how long does it take for the patient to present from the time of symptom onset? So, I don't know if you have a sense of that as far as getting neurosurgery involved or potentially reversing that patient? Thoughts on that?

Dr. Kreitzer:

Yeah, I think, you know, the way that posterior fossa ICH is deadly, of course, is because it obstructs at the fourth ventricle, and then patients ultimately die of brainstem compression, hydrocephalus. So, really the first things to look for there are deterioration in mental status, usually they'll get sleepier before anything else. So, you know, those are the patients to get quickly to a comprehensive stroke center or to a place with neurosurgical capabilities to monitor for the need for that SOC, or to do it immediately. Any other thoughts from the panel?

Dr. Gibler:

What are your thoughts about that? Rhonda?

Dr. Cadena:

So, for cerebellar hemorrhages, we typically get neurosurgery involved right away because those patients are going to benefit from the surgery. And so, I'm assuming this is also on patients who are anticoagulated, that's number one, first of all reversal of anticoagulation, but those are just very high-risk hemorrhages and so neurosurgery should be involved from the very beginning.

Announcer:

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