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Development of a Care Pathway Using Specific Reversal Agents for Anticoagulated Patients With ICH

Announcer:

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Dr. Gibler:

Dr. Parry-Jones is a Stroke Neurologist, well known by everyone in this group, and far outside of this group. So we very much appreciate your being here as well. He is from the Geoffrey Jefferson Brain Research Centre at the University of Manchester in Manchester, UK, and has a tremendous experience, which I think will be fascinating to hear about this discussion of bundling of care because I think you have hypertension as one of the significant issues, well, what about blood pressure control, and these are things that everyone in this room knows that this is important. But I wanted Adrian to present this and talk about his care bundling and how they should work for these patients, expanding out to a large patient population.

Dr. Parry-Jones:

Right, thank you very much. So yeah, I'm going to talk about the sort of practicalities of delivering acute care, particularly focused on anticoagulant reversal. So if you were in the previous session, it was a very exciting day for intracerebral hemorrhage. So I think we had two positive trials showing benefit for treatments for intracerebral hemorrhage. So I'm just going to go through with just a general conceptualization of how we can think about treating these patients, just as sort of hang the anticoagulant reversal on to that.

So patients present with a bleed in the brain. The majority don't expand. But if and if they don't, there's a process of secondary injury which occurs around the hematoma and you see that manifesting radiologically as edema. Then over time, the hematoma is gradually cleared away. Now obviously, what we're worried about is this problem of hematoma expansion, and that obviously causes mass effect, it increases the injury to the tissue around it, and it worsens secondary injury and the outcome for the patient.

As we know, as of the talk earlier, hematoma evacuation can be of benefit to patients. And, you know, getting the blood out of the brain will reduce the edema and will potentially reduce the secondary injury as well as the mass effect.

So what can we do to reduce the risk of hematoma expansion? Well, we know that anticoagulation reversal will help with that. But there's also evidence from the combined meta-analysis of all the studies that have targeted blood pressure in the first 7 days after ICH, that it does reduce hematoma expansion as well. So thinking about the problem of hematoma expansion, of course, there, conceptually all hematomas must expand initially. So they start at a point, they get big enough to cause symptoms, and the patient calls for help. They get brought to hospital, they haven't an initial scan, and then a proportion of them will have this subsequent expansion which occurs in hospitals. So that's what we're talking about here, really. Now it occurs in around 20% of patients. The key clinical predictors for it are the time since the onset of symptoms, the size of the hematoma, and whether or not they're taking anti-thrombotics. So particularly anticoagulants, but also anti-platelets, there are imaging predictors of this, so the spot sign, and then there are some non-contrast CT signs, such as the blend sign, black hole, sign, and so on, all of which tend to demonstrate that there's been fresh recent bleeding and

therefore a higher risk of expansion.

So the other positive trial this morning was INTERACT3. So this has shown the idea that taking a care bundle approach to managing these patients is associated with improved outcomes, or leads to improved outcomes. So this is something we've been doing for some time at the center that I work in Salford, and we've been gradually spreading to two other centers in our region and subsequently across the north of England. So we've put things together as the ABC care bundle here, so anticoagulant reversal, blood pressure lowering, and we put together a care pathway to refer the right patients very promptly to neurosurgery, and to avoid referrals when they're not really required.

So focusing first on anticoagulants, the graphs that I'm showing you here are the proportion of patients per quarter in our National Audit Programme Data that are taking anticoagulants. So the dark blue is those not anticoagulated. The green color is those on DOACs, and the pink color is patients on vitamin K antagonists. So you can see that consistently over time about 20 to 22% of intracerebral hemorrhages will be taking some form of anticoagulation, but over time the DOACs are really becoming the predominant ones. So what can we do about it? You've heard a lot about this already. So vitamin K antagonists, we want to give prothrombin complex concentrate to replace the clotting factors that are missing and also give vitamin K. Dabigatran, or idarucizumab as a specific reversal agent. And for factor Xa inhibitors, the ESO guideline recommends andexanet alfa as a first-line treatment for patients taking apixaban or rivaroxaban, and prothrombin complex concentrate can be used for edoxaban and where andexanet alfa is not available.

So essentially, if you get a reverse anticoagulation, you probably should do it as quickly as possible. And we should really think about this like thrombolysis. Because what you're dealing with is a background risk of hematoma expansion, and the longer you wait to treat, the longer that risk persists. So it's important to break down the whole care process into steps. Obviously, there's the time to get the patient to hospital, scene-to-door time, the time to get that patient in the scanner, the door-to-scan time, and then the time from the scan to delivering treatment. So in thinking about all of this, it's really important that you monitor data and collect the times for these specific steps in the process, and then apply quality improvement methodology to try and make all of those steps as short as possible. So the things that often lead to delays are rapid brain imaging on arrival, because of course you don't know they've had an intracerebral hemorrhage until you scan them. So you have to make sure that people are asking up front about whether or not people are taking anticoagulants when they come in with a suspected stroke. You need to try and make a quick decision on treatment. Establish when the last dose was taken and the patient's onset time as well, because it's very important to know how far in the disease process you are too. Having your protocols as simple as possible, and removing unnecessary steps is also a really important thing to do.

And finally, it's important that you have easy access to these treatments.

So some work that we did previously to improve reversal of vitamin K antagonists, we basically introduced three key changes which lead to an approximate halving of the treatment times for them. So first of all, we used to have to collect our prothrombin complex concentrate from the blood bank, which was some distance away from the emergency department. And there were a lot of administrative steps to do before you could do that. So what we did was have a stock enough for one patient kept in the emergency department that was there for immediate use. That was one of them. We introduced point of care INR testing. And finally, we agreed with hematology that we could deliver PCC without referring every case to them, which we used to have to do, which would add an unnecessary delay.

In terms of using specific reversal agents, they're generally simpler to give than PCC, so this is the dosing chart for andexanet. We obviously discussed this briefly in the last panel. When you draw this up, it comes in vials of 200 mg, which has to be reconstituted and then a bolus is given initially followed by an infusion. This can be stored in a fridge so it doesn't need to be in blood bank so you can have it more readily accessible which can be an advantage over PCC. With idarucizumab, similarly, it's a standard dose of 5 grams, which is given as two vials, each with 2.5 grams in it. It's already reconstituted and ready to administer. So you can transfer it to a syringe and give it as a bolus or it can be delivered as an infusion. So it's generally much quicker to give than PCC.

So other things we've done to speed up care is that we introduced a pre-hospital pre-alert for patients on anticoagulants. So now if our ambulance crews pick up a suspected stroke, out to 48 hours who's taking an anticoagulant, they're pre-alerted. All other strokes, they were only doing it within 4 hours at the time. So when we did this, this led to a 30-minute reduction in the door-to-scan time because those patients were met at the door and very rapidly putting the scanner.

So as part of the introduction of the care bundle and making all of these changes, we saw quite a big reduction in mortality at our center. So we went from a 30-day case fatality of 35.5%, down to 24.2, which is a 10-percentage point drop. So all of these things contribute to that.

So just to summarize, anticoagulant reversal is a key part of delivering a hyperacute care bundle in ICH. It was part of the INTERACT3 bundle which you all have heard this morning. Unlike the INTERACT3 trial, about 1% of patients were taking anticoagulants and in many of our systems it'll be around 20%, so maybe a much more important component. Delays in treatment increase the risk of

expansion, and it's really important to monitor your data regularly so you can improve the processes.

Announcer:

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