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Life-Threatening Bleeding in the Anticoagulated Patient: Real World Evidence

Announcer:
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Dr. Kreitzer:
Hi, my name is Natalie Kreitzer. And I'm an Associate Professor of Emergency Medicine and Neurocritical Care at the University of Cincinnati where I also work with the UC Stroke Team. I'm going to speak today about life-threatening bleeding in anticoagulated patients, specifically with patients with intracranial or intracerebral hemorrhage and go through some of the real-world or newer evidence that has emerged over the past couple of years.

Now to get us started, I just want to introduce a little bit of background concept, which is the concept of hemorrhagic expansion. And we know that with ICH, a lot of patients have hemorrhage expansion, but when they're anticoagulated, this risk is significantly increased. And we have here on the slide, what can happen with hemorrhage expansion. This traditionally happens within the first few hours after a patient is last seen well or has the onset of symptoms. And this is associated with worse outcomes.

Now I have here on this slide, some analyses from Davis, which was published in 2006 in *Neurology*. Now, this demonstrated the outcomes that are associated with hematoma expansion. And I want to direct your attention to those first three lines of the table. The first of course, is the baseline ACH volume. And we know that that's significantly associated with outcomes, both mortality, as well as modified Rankin Scale, which is more of a clinical outcome of how patients do at 6 months. And then on the second and third lines, we look at that change in the size of hematoma or hemorrhage expansion. And regardless of whether we're looking at a percent change in ICH volume, or an absolute change in ICH volume, not surprisingly, that is associated with clinical outcome as well as mortality.

So we want to do what we can to stop that hematoma expansion. Now, when we think about direct oral anticoagulants or really oral anticoagulants in general, the anti-Xa agents are by far the most common and they're growing in popularity and becoming more and more common each year. Now, andexanet alfa is the reversal agent that has been approved by the FDA for anti-Xa agents. It is a decoy molecule, which mimics native factor Xa.

Now, ANNEXA-4 was published in 2018, which led to the FDA approval of andexanet alfa. In this study, I have a few bullet points describing that but basically describes this use of recombinant modified human decoy factor Xa protein in patients with active ongoing life-threatening hemorrhage. It was given to patients if they had a last dose within the past 18 hours of an anti-Xa agent. And the labs at follow-up, which was one of the primary endpoints, was the anti-Xa level. Now the dose differs depending on the Xa inhibitor dose and the time the patient took that. Now, since one of those primary endpoints was looking at that lab value, comparing it from baseline to post infusion or even just after the bolus, and that demonstrated 90 to 92% reversal, the FDA did approve the andexanet alfa.

But despite that there were a number of limitations and concerns with this study. The first of course, is this was a single-arm study without comparison. It was non-randomized, it was only active, life-threatening hemorrhage patients. Many of the participants were reversed many hours after they were last seen well. So concern being that they had escaped that first few hours when we know that

hematoma expansion is most likely to happen. As I mentioned, one of the lab values was - or one of the endpoints was a lab value. It was also criticized because many of these patients have smaller hemorrhages and a high GCS to begin with, with a thought that they may have done well regardless. And then, of course, the risk of thromboembolic complications was discussed within this trial. So it became pretty evident that more data was needed, which is what I want to talk about next.

Now, one of the criticisms, as I mentioned, was that one of the primary endpoints was a lab value rather than hematoma expansion. So a couple of studies have looked at this question specifically using retrospective data. So the first one I present here is by Costa, this was published in 2022. And this was a propensity score analysis. So patients were basically paired with each other, if they'd received 4-factor PCC from a different study or if they'd received andexanet alfa within the ANNEXA-4 study. Baseline factors such as ICH volume, age, and other factors that were associated with outcomes that patients after ICH were used to match patients. And basically, the propensity score methodology tries to replicate as best as possible a randomized controlled trial utilizing retrospective data. Now, the study did find that there was a significant difference in hematoma expansion with fewer patients experiencing hematoma expansion in the andexanet alfa treated group compared to the 4-factor PCCs.

Similarly, a second propensity score analysis was published last year as well by Huttner in *Stroke*. And this was a very similar concept to that previous study. And they even use the andexanet alfa cohorts. And these were matched with patients who received usual care, which was generally 4-factor PCCs, when they had an anti-Xa-associated intracerebral hemorrhage. And what they found was, again, similar to the previous study 13% ICH expansion in the andexanet alfa group, compared to 36% who experienced hematoma expansion in the PCC or usual care group. And this was a significant difference with a P value of 0.005. When in-hospital mortality was looked at, there was not a significant difference, although the P value was only 0.06.

Now the study that we're all waiting to see the final results from is ANNEXA-I. And this is a phase 4, multicenter, international, randomized controlled trial comparing usual care, which is generally 4-factor PCCs to andexanet alfa in patients who have intracerebral hemorrhage associated with an anti-factor Xa DOAC agent. This is a randomized controlled trial. And the protocol states that these are patients who were last seen well within under 6 hours, and within 15 hours of that last DOAC dose. So really getting at those patients who truly do require reversal for their anticoagulation. The endpoint of this is hemostatic efficacy, which is adjudicated by a third party looking at the percent hematoma expansion in both groups. Now, there had been a planned enrollment of 1,200 participants in this trial. However, in May, the DSMB recommended the trial to stop early after only 450 participants. And this is because of efficacy, meaning that the 4-factor PCC patients had higher rates of hematoma expansion compared to the andexanet alfa group. Now, certainly more information is coming. This announcement is all that has been made at this point. But certainly, we are all eager to see the final results.

And another recent study that just came out in May that was presented at the European Stroke Conference, looks at anticoagulation reversal when we take it into context of all the other factors that we know influence the outcome of patients with intracerebral hemorrhage, and this is the INTERACT3 trial. This was also a positive study. And this basically describes that patients who receive a bundle of care that consists of blood pressure control, anticoagulation reversal, fever management, and glucose management all acutely after an ICH have improved outcomes at 6 months compared to those who do not receive the bundle of care.

Thank you very much for your attention.

Announcer:
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