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KDIGO Conversations in Nephrology: Maximizing Filter Life During CRRT – Best Practices on Anticoagulation and Citrate Use

Announcer:
Welcome to KDIGO Conversations in Nephrology. This episode is titled "Maximizing Filter Life During CRRT – Best Practices on Anticoagulation and Citrate Use."

Here's your host, Dr. Ravi Mehta.

Dr. Mehta:
How does one go about maximizing fertile life during CRRT? Today, we discuss best practices on anticoagulation and citrate use.

Hello, and welcome to KDIGO Conversations in Nephrology.

I'm Dr. Ravi Mehta, Professor of Medicine at the University of California at San Diego, and on the program with me today to discuss maximizing fertile life during CRRT is Dr. Ashita Tolwani. Dr. Tolwani is a professor of medicine at the University of Alabama in Birmingham in the United States. Her recent interests include acute kidney injury, ICU nephrology, and CRRT, and she is an expert on citrate anticoagulation, so certainly the perfect guest for our topic today.

Dr. Tolwani, welcome to the program.

Dr. Tolwani:
It's an honor to be here. Thank you so much for inviting me.

Dr. Mehta:
So, Ashita, to start, why is the circuit patency and integrity important for CRRT, and what are the key issues that we should consider?

Dr. Tolwani:
CRRT stands for continuous renal replacement therapy, so to provide effective solute clearance and fluid removal, it really needs to run uninterrupted. And we know that decreased circuit patency results in significant time off the CRRT device, and this has adverse consequences such as decreased delivery of dose, decreased fluid removal goals, increased loss of blood if you can't return the blood when the filter clots. It also increases the burden for the nurses, who need to keep replacing the filter, and increases cost because extra filters are used; you have wastage of CRRT solutions, too.

So making sure the circuit stays patent is very important, and there's several characteristics that you have to consider that affect circuit patency. I would say probably the most important is the vascular access. Vascular access dysfunction is a very common cause of delayed circuit life, so it's very important you have the correct catheter length for the correct position, and the tip should be in the correct location. The best catheters that work for CRRT are a right IJ catheter. Other things that affect circuit patency are really circuit-related factors. Adding stopcocks to the system increases resistance. You know, many of the CRRT devices have a deaeration chamber, and that air-blood interface can cause clotting if you don't have a proper layering of fluid. Nursing delays in addressing alarms also can cause increased circuit clotting because the blood pump continues while the other pumps do not, and that can contribute to filter clotting, especially since the patient won't be getting an anticoagulant.

The mode of therapy also affects circuit patency. With convective therapy, since you have high ultrafiltration rates and you're pulling plasma through the filter, you have increased viscosity by the end of the filter with increased hematocrit, and this can be prone to clotting. We measure this effect by something called filtration fraction. Filtration fraction is the fraction of plasma that is removed from blood during hemofiltration, and it ideally should be kept less than 20%-25% to decrease the chance of circuit clotting. With convective

therapies, the way to do this is by either using an increased blood flow rate or by using more predilutional replacement fluid. Finally, even if you have optimized all these circuit characteristics, you still have increased clotting of the circuit because exposure to an extracorporeal circuit activates a clotting cascade. So insufficient anticoagulation is a big deal.

Dr. Mehta:
So thank you for bringing out these really important elements for the circuit. Given that anticoagulation techniques are present and so variable, how do you decide which one to use, and is it really necessary to use anticoagulation?

Dr. Tolwani:
There have been described in the literature no anticoagulation protocols having effective circuit patency, and you can definitely maintain circuit patency by optimizing all those circuit factors we just talked about, like the access, the circuit issues, etc. But even if you have a circuit patent, that doesn't mean that you're actually delivering the proper dose of therapy, because we know over time, the filter permeability decreases, and this decreases the diffusive or convective loss of solutes through that filter. Essentially, it decreases your solute delivery, or I should say dose. So given that, I recommend that anticoagulation should be used for that purpose. The most common anticoagulants used for CRRT are unfractionated heparin and regional citrate anticoagulation [RCA]. Other options you may see in the literature are unfractionated heparin with protamine, low molecular weight heparin, thrombin antagonists, heparinoids, or platelet-inhibiting factors.

We all are familiar with unfractionated heparin. It's easy to use, has a short half-life, we all know how to use it, but we know there's significant disadvantages, too. It has unpredictable pharmacokinetics, so that results in, you know, dosing variability. There's a risk of heparin resistance to the low antithrombin levels, the development of potentially heparin-induced thrombocytopenia. But I think the biggest drawback of systemic heparin is the risk of hemorrhage – systemic hemorrhage of the patient – and we know by multiple studies that it really does increase life-threatening hemorrhages for these patients.

So that's why citrate has become more common, because it's a regional anticoagulant. So, basically, the way citrate works, it chelates ionized calcium, and if you look at the clotting cascade, free calcium is required at every step. So if you get the ionized calcium low enough in the circuit, the filter cannot clot. So the optimal level is an ionized calcium less than 0.4 millimoles per liter. And that effect of the anticoagulant is reversed by providing a calcium infusion back to the patient and keeping the ionized calcium in normal levels. So that's how citrate works and why it's a little bit better than heparin because it doesn't have the systemic effect.

Now, when you're really choosing an anticoagulant for the patient, it should be individualized. It should be based on not only the patient's condition, but also the availability and expertise at the institution. So, essentially, you really need to focus on safety of the patient. So patients who cannot tolerate anticoagulation because they have a high risk of bleeding, a regional citrate anticoagulation, if you have the expertise, would be preferred. In patients who have normal or moderately disturbed hemostasis, then using heparin would be probably appropriate. In patients with heparin-induced thrombocytopenia, you may consider argatroban or bivalirudin. But no matter which anticoagulant is used, you would change it according to your patient's condition and your expertise.

Dr. Mehta:
That was very helpful. Given that regional citrate anticoagulation is now increasingly used and is being recommended as a preferred method for anticoagulation, is there adequate evidence to support this?

Dr. Tolwani:
There is. There have been multiple randomized trials now comparing regional citrate anticoagulation to heparin, and most of them have suggested that citrate provides increased filter patency. In fact, there was a meta-analysis published several years ago of 11 randomized trials in nearly 1,000 patients, which showed that the risk of circuit loss was lower with RCA and that you had decreased bleeding. And by the way, this was recently confirmed in a large German multicenter study of over 600 patients. And it's for these reasons that KDIGO has recommended the use of citrate as first-line for patients with AKI needing CRRT.

Dr. Mehta:
I know, Ashita, you have utilized RCA protocols for citrates safely and effectively for many years. What are the parameters that should be monitored both for circuit integrity, and how frequently should these be done to assure the best performance?

Dr. Tolwani:
Okay. Well, first of all, I want to say that RCA is available for all CRRT modalities. And even if the patient is systemically anticoagulated, you should still use RCA because you want complete control of the circuit. You don't know what's going to happen with the systemic anticoagulation, when it's going to be stopped, etc. So we use it even in patients who are systemically anticoagulated. So when you give RCA, it can be delivered as a fixed ratio between the blood and citrate infusions or titrated based on ionized calcium levels. Many of the CRRT machines these days have RCA software that allows for safer and easier delivery of the RCA, but

unfortunately, it's not available everywhere, including the United States. Given that, it's really important to know all the different components you have to think about when developing a citrate protocol.

The first component, of course, is a citrate solution. Citrate solutions can be classified as either hypertonic – they have a high level of sodium and they're concentrated – or basically physiological solutions that have a normal concentration of sodium. The hypertonic solutions are administered as a separate citrate solution and is distinct from the replacement or dialysate solutions, while the isotonic solutions with the physiological sodium content are dilute and are used as an anticoagulant and a predilution replacement fluid. Depending on which CRRT solution is used, you have to choose what type of CRRT other solutions to use dependent on the citrate choice. For instance, if you use some of the hypertonic solutions, you may have to use hyponatremic solutions for CRRT, like a replacement fluid or a dialysate, or even a lower buffer concentration since citrate is converted to bicarb by the liver. When using the isotonic dilute solutions, you can use a commercially available solution without any issue.

The other thing to be aware of is the potential complications of RCA. These include hypernatremia, depending on the citrate solution you use. Since citrate chelates calcium, you can have hypo- or hypercalcemia. Citrate also chelates magnesium, so you can have hypomagnesemia. And of course, since citrate is converted to bicarb when the liver is working, there are acid-based disorders you have to be aware of. Most of the time when you're monitoring for citrate, most protocols monitor blood electrolytes, including the circuit and systemic ionized calciums, at least every 6 hours, or more frequently if there are changes made or if there is concern for accumulation of citrates. The bottom line is that in order to have a proper RCA protocol, you need a comprehensive algorithm of how to adjust the rates of the different components, to prevent or correct for any of the acid-based abnormalities.

And finally, one last thing I just want to say is that patients with severe liver failure or lactic acidosis may have difficulty in metabolizing citrate, so you need to be able to recognize citrate accumulation and how to correct for it.

Again, RCA has been used safely in patients with advanced liver disease and with lactic acidosis, and these metabolic complications can be avoided if you use really strict protocols, appropriate training, and of course, safer citrate solutions and integrated citrate software, if you have that availability.

Dr. Mehta:
Thank you for sharing those. For those just joining us, this is a KDIGO Conversation in Nephrology. I'm Dr. Ravi Mehta, and I'm speaking with Dr. Ashita Tolwani on maximizing fertile life during CRRT – best practices on anticoagulation and citrate use.

So Dr. Tolwani, what have been the challenges you've seen during the pandemic with maintaining the circuit integrity, as I believe this has been a major issue reported in the literature?

Dr. Tolwani:
That is correct. It has been very challenging. There are patient-related factors and technique factors that make this so challenging. The patient-related factors, of course, are that these patients often are hypercoagulable, and this can be from the cytokine storm or other reasons. During this time, we also wanted to limit nursing exposure and use of PPEs, so that related to issues with maintaining CRRT circuit patency also. For instance, this meant decreased manipulations of the CRRT device, so, you know, we had alarms that lasted longer to prevent nurses from having to go in frequently. We ourselves, at our institution use extension tubing, so all our CRRT machines were outside the ICU rooms, and because of that, this led to increased clotting of the circuit. Other challenges in this patient population is use of prone ventilation with issues with the access placement. We had lots of issues with access dysfunction.

So how we manage these challenges were all different ways. First of all, it was very important that we ensured a proper access in the right IJ. Many places, if they were using convective therapy, made sure they used higher blood flows to decrease the filtration fraction or even converted to diffusive therapy. But I think what came out of this pandemic is a realization that these patients need anticoagulation.

There really has not been a single anticoagulant regimen that has been shown to be better for these COVID patients, and people have tried all different things – anything from regional citrate anticoagulation to systemic heparin to thrombin inhibitors. When we used extensions, we had to use a combination of citrate and heparin to keep the circuit patent, and this was in predominantly all our patients who had extensions. When we stopped using the extensions, however, we were successful, in over 90% of our patients, keeping the circuit patent just with citrate.

Dr. Mehta:
So this has been great to see how you adapted your anticoagulation and circuit strategies for the COVID pandemic. Finally, what would be your recommendations for clinicians to optimize the effectiveness in their own institutions?

Dr. Tolwani:

Well, I think it's always important to take into consideration all those circuit factors we talked about. You need a well-functioning vascular access. If you're using convective therapy, higher blood flows, or using a predilutional fluid to reduce the filtration fraction, making sure you decrease the blood-air contact in the bubble trap and promptly reacting to alarms. If you're using an anticoagulant, regional citrate anticoagulation, RCA, is recommended if you have the expertise or the availability of the solution. Regardless, though, of whatever anticoagulant you're using, it's really important to have standardized protocols and order sets, because those are the keys for multidisciplinary management. And then, you have to have a quality improvement program. You need to monitor the down time and provide periodic measurement of solute clearance to ensure that you're providing good therapy and delivering CRRT as it should be delivered.

Dr. Mehta:
With that takeaway in mind, I want to thank my guest, Dr. Ashita Tolwani, for joining me to discuss best practices on anticoagulation and citrate use during CRRT. Dr. Tolwani, it was great having you on the program.

Dr. Tolwani:
Thank you so much. It was a privilege being here today.

Dr. Mehta:
I'm Dr. Ravi Mehta. To access this and other episodes in our series, visit kdigo.org/podcasts. Thanks for listening.

Announcer:
This episode of KDIGO Conversations in Nephrology was provided by KDIGO and supported by Baxter Healthcare.