**The Why, How and What of Citrate Anticoagulation**
Ashita Tolwani, MD

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| Speaker 1: | 00:00 | Good afternoon everyone. it's my pleasure to start this session on citrate anticoagulation for CRRT quite humbled to be sitting next to Dr. David Ward who invented citrate anticoagulation and, Stue Goldstein from Cincinnati Children's Hospital and Dr. Ward will introduce our first speaker. I'm humbled to be sitting besides Stue Goldstein is one of the great leaders in pediatric nephrology. So with that said, we're also delighted with the,people who are going to be speaking at this symposium on citrate anticoagulation for CRRT. The first speaker is Ashita Tolwani who, did some retraining in University of Alabama where she is now a professor and a leader in critical care nephrology. And she also has a MSC from Harvard and, a lot of publications and advances in the area of CRRT. So, I think you told me you've got 25 CRRT machines running at this moment, something like that. Correct? |
| Speaker 2: | 01:14 | Thank you. It's actually an honor for me to be here with both of you and at this conference and to be truthful, I have been coming to this conference for years. And I've actually learned from everybody here. So it's been a privilege. So I'm just gonna open up for my other speakers about why, how, and what of citrate anticoagulation. Just to give a brief overview of the mechanisms and my other speakers are going to elaborate on the concepts. So first of all, I would like to tell you that citrate definitely has a very long history here. It's been used for plasma pheresis for multiple years since the 1960s and also intermittent hemodialysis. But it was actually revolutionized here mainly by Dr. David Ward, who I have the privilege to sit next to you in terms of where it was invented for a citrate for CRRT back in 1989 is my understanding. |
| Speaker 2: | 02:12 | And here is the actual paperwork where the formulations were made. And this is definitely set off the predominant use of citrate used universally now. And so this was apparently a patient with heparin induced thrombocytopenia and essentially citrate was used successfully on this patient and the patient made a full recovery. And so it's been exciting to see this. This resulted of course in the paper, done by San Diego regarding their citrate protocol with 4% trisodium citrate. And this is essentially a closer look at their protocol, which will use a 4% trisodium citrate with CVV HDF. A dialysate that is consistent of sodium of one 117 mEq/L in the post filter fluid, and since then citrate, is definitely expanded. So I know that when we started |

our citrate protocol, it was after I attended the conferences here and learnt from the experts extensively.

Speaker 2: 03:13

So with that, why citrate? Well, besides the fact that it's been done here and they did a great job, it actually is been recommended by the KDIGO guidelines. If you look at these guidelines that were published several years ago, based on the literature that has come out over the last 10 years, they pretty much say that citrate should be used for patients who need to be anticoagulated for CRRT. So where's the evidence for that? Well, I won't belabor this presentation with all the multiple studies that have been done, but essentially there've been multiple randomized control trials comparing citrate to either low molecular weight heparin or to systemic or unfractionated heparin. And this is a meta-analysis looking at 11 such randomized controlled trials of nearly 1000 patients. And what this meta-analysis showed is that there is definitely less circuit loss that was statistically significant with citrate, less bleeding, no changes in terms of mortality and no concerns for metabolic alkalosis, which is one of the side effects of citrate.

Speaker 2: 04:19

So there is definite evidence supporting the use of citrate in the literature by good trials. So given that, how does citrate work? Why is it so effective? Well, this is a depiction of the anticoagulation cascade. And as you can see, calcium or free calcium is required for every step or nearly every step. So the main concept is that citrate chelates calcium, and so essentially for citrates provided to the extracorporal circuit, it chelates free calcium, prevents the activation of these calcium dependent procoagulants and you can measure this effect by the ionized calcium level in the circuit. And when the calcium citrate returns back to the patient, it's metabolized mainly by the liver. And the anticoagulation effect is reversed by providing a calcium infusion when citrate in free calcium bind of course as measured as total calcium. And this becomes important when talking about some of the complications of citrate and potential citrate accumulation, which will be discussed in some of the other lectures today.

Speaker 2: 05:26

So how is citrate metabolized? Typically has a plasma half life of five minutes but can be prolonged in renal failure to 20 minutes. And essentially if you use trisodium citrate, the main metabolism organ is the liver. It can also be metabolized by the kidney in muscle cells and potentially if the liver is working. One mole of trisodium citrate can be converted to three moles of bicarb. So citrate can provide not only an anticoagulant effect but of course a buffer. So just to give you perspective, normal blood levels of citrate are approximately 0.05 millimoles per

liter. And studies have shown that bleeding time can be prolonged infinity at citrate levels of 3 to 5 millimoles per liter or corresponds to ionized calcium level less than 0.35 millimoles per liter

Speaker 2: 06:16 So levels of 12 to 15 millimoles required for stored blood. And reason this is important is to understand that a lot of times blood products that you're giving in terms of fresh, frozen plasma, etceteras can also alter systemic ionized calcium results in patients on citrate. So citrate itself as a very, very small molecule. It's a size of urea and the sieving coefficient which is a reflection of how permeable the molecule is through the membrane is about 1 So it's clear very easily whether you use convective or diffusive therapy. And essentially the clearance depends on the citrate concentration, the filter, the filtration fraction, and of course your flow rates. Also just to let you know about 40 to 60% of citrate is cleared on the effluent based on standard effluent rates that are used today.

Speaker 2: 07:12 So you can see already that citrate anticoagulation provides distinct advantages. It's regional, you only anticoagulate the circuit so you avoid the bleeding complications of unfractionated heparin and the other systemic anti-coagulants. It doubles as a buffer, which can be a good thing or a bad thing depending on your level of acidosis or alkalosis. It's highly effective in studies as I've already demonstrated or presented to you in the meta-analysis. And it's not associated with thrombocytopenia, mainly does not cause heparin induced thrombocytopenia. But there are some disadvantages that have made it not as widespread. And one of them is of course the metabolic complications which will be discussed in the future lectures and also it can cause or basically results in complex protocols depending on which citrate formulation you use and which CRRT modality you use. So that comes to the next topic. Which citrate protocol are you going to opt to use? And this depends on your citrate solutions, the method of citrates delivery, and CRRT circuits options, which I'm briefly going to go over. And again, these will be discussed more in detail with the next two talks.

Speaker 2: 08:33 So these are the most commonly available commercially available citrate solutions, a worldwide of course in the United States, citrate is not been approved for an anticoagulant by the FDA for CRRT and so essentially the United States, the first two citrate formulations are what's commonly used and these are used for blood banking. So you have the 4% trisodium citrate, the ACD-A, which is a 2.2% solution , outside the United States.They have now developed a more dilute citrate solutions

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| | | that are isotonic and serve not only as an anticoagulant, but also as a replacement fluid for patients who are undergoing convective therapies. So just to get a show of hands here, and I always ask this question, how many were using citrate in your program today? How many of you at this time are using the 4% trisodium citrate? |
| Speaker 2: | 09:34 | Excellent. ACD-A? I see a little bit more hands. What about some of the other ones specifically if you're not from the United States? Anyone using prismocitrate Okay. Any other formulations? |
| Speaker 2: | 09:51 | Excellent. So if you look at the various citrate protocols published in the literature, you can get pages and pages of protocols that have been listed using different citrate formulations, different modalities of CRRT, but the main thing is this, all protocols have in common is how much citrates delivered, which is despite all the different formulations use, the amount of citrate delivered is about the same. It's about 2 to 6 millimoles per liter. Most people target between 2 to 3 millimoles per liter citrate for the blood. And this correlates with an ionized calcium level of less than 0.4 millimoles per liter. |
| Speaker 2: | 10:33 | Finally, what about citrate delivery? It can be done two different ways and you'll hear about automated citrate devices in the next talk. It can be given as a fixed relationship between the blood flow and citrate or it can be titrated based on ionized calcium levels. So essentially if you know the concentration of citrate you're using and your blood flow rate, you can mathematically calculate how much citrate is needed to keep the citrate level in the blood, either 4 millimoles per liter as in the left chart or 3 millimoles per liter. Or you can actually have or use charts that are published like this that tell you how to deliver citrate based on your blood flow. These are just starting points and typically what I hear for ACD -A is most institutions start at a dose of 1.5 times the blood flow and they can see on this chart that's about 150 milliliters per hour, but one 59 is what gives you a blood level about 3 millimoles per liter. |
| Speaker 2: | 11:36 | How many of you use a fixed method for citrate delivery? Okay. The other option of course, is titrating the citrate by postal filter ionized calcium. So in this method? methat, Essentially what happens is the citrate is given, widely the access point prior to the circuit. And typically if you're using diffusive therapy, the calcium free dialysate is used. But that's not necessary. The post filter ionized calcium is then measured to keep it at therapeutic level. When the blood returns back to the patient, the calcium and citrate is metabolized by the liver, essentially the citrates |

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| | | are converted to bicarb. The calcium is released to the patient and yet a systemic calcium infusion is provided to keep the patient's ionized calcium on normal range and replace the calcium lost in the circuit and that's essentially how the titration works. Okay. If you look at the CRRT RCA, regional citrate, anticoagulation options based on circuits. |
| Speaker 2: | 12:48 | Really it's about the same despite what modality of CRRT you use. It's always given prior to the filter and can be given as a separate concentrated solution or in combination, as I mentioned, as a dilute solution that can be provided for convection. So these are just some protocols that I have just listed in this slide set. Just to let you know that there's various options with different modalities. This is a protocol that was published in Florida using convective therapy with ACD-A. It gives you an idea of their solutions they use and how they target their protocol. This is of course what I believe UCSD has evolved to, at least this was provided to me by Dr Mehta and of course they're using the 4% trisodium citrate and use a CVV HDF modality. This is what South Carolina does. Very similar CVV HDF, except they use ACD-A. And again, I'm not belaboring these protocols. I just give an examples of what's been published out there in the literature and how many different formulations that have been successful in options. At UAB, we typically use a dilute citrate formulation. We also do CVV HTF. |
| Speaker 2: | 14:07 | So in summary, and this is setting the tone for my wonderful next speakers, is that regional citrate anticoagulation has emerged as an effective way of anticoagulating blood during CRRT. There's plenty of evidence in literature supporting it at this time. Now that we have availability of simplified RCA protocols as well as the development of CRRT devices, which we will hear about with integrated infusion systems and dedicated software. We can increase the safety and use of RCA, but we still need to be aware of the metabolic complications, which will be discussed in detail. So thank you very much. |
| Speaker 3: | 14:50 | Will take some time to answer questions, does anybody have questions for Dr. Tolwani. |
| New Speaker: | 14:50 | i Have a question actually 1 or 2, and we are citrate users and in the United State, we have to deal with calcium shortages and its easier to get cilaros in the country than to get something of the periodic chart of the table of element how do you |
| Speaker 2: | 15:37 | We did it's a protocol that's definitely not as versatile as a current protocol we use, but in the situation of calcium shortage, it has served us well. We store a lot now though. And |

we came up with a protocol using ACD-A and using a calcium containing already available CRRT solution with the calcium concentration of 3 ml per liter. And we calculated how much we needed to provide for as opposed filter replacement fluid to both provide dose into effectively provide enough calcium to replace the calcium losses through the effluent. Now again, there are limitations to that particular protocol. We did publish it, but definitely was much better than our circuits clotting every 20 minutes.

Speaker 1: 16:28 Right. Great. And then could you also speak to, the choice that people have to make currently until we have a more balanced solutions? What are the pros and cons of using trisodium citrate versus ACD-A? What are the things that you have to look at? Just a little bit.

Speaker 2: 16:47 Okay. So, I think that this may be what some of our other speakers get into, but essentially, from our perspective, you know, 4% does contain a high amount of sodium concentration. I believe in like 408 ml per liter in the sly. While ACD-A is a solution that contains 220 ml of sodium. So in the past, given the sodium concentration in the trisodium 4%, often before you had more of these commercialized solutions, you would have to use perhaps hypertonic other CRRT solutions. But I don't see that used as often. I think the key is that if you use a very low blood flow rate, you can get by with less citrate to achieve your therapeutic levels in the blood and therefore mitigate some of the systemic complications. There's also issues with the calorie content, etcetera, but I think they will be discussed more in the metabolic complications.

New Speaker: 17:45 Just wanted to set up Dr Ostermann.