

## Citrate Protocol for Continuous Renal Replacement Therapy

### **Why is it used?**

Citrate is used when we need to anticoagulate a filter but do not want to systemically anticoagulate the patient. Citrate provides regional instead of systemic anticoagulation (anticoagulates the filter only). The protocols used for citrate administration are different between UH and VH. Nurses in CCTC have not been trained to utilize the protocol that is in use at UH; only the CCTC protocol should be implemented at VH.

### **How does it work?**

Calcium is important in several steps of the clotting cascade. Using a PrismaFlex™ machine, citrate is administered via the PreBlood Pump (PBP), which means the blood is anticoagulated as soon as it is pulled from the access port. Citrate chelates (or bonds with) ionized calcium (ionized calcium is the charged and biologically active form of calcium that is found in the plasma). We adjust the citrate infusion to achieve a very low **post filter ionized calcium (initially 0.25-0.35 mmol/L)** to prevent blood from clotting in the filter.

The chelated calcium and the citrate enter the filter and diffuse into the dialysis fluid where most of the citrate and calcium-citrate is removed. The calcium that is removed through the filter is replaced with a systemic infusion of calcium chloride to maintain normal systemic ionized calcium levels.

Calcium chloride is titrated to achieve a steady state between the citrate that enters the systemic circulation and the rate of hepatic citrate metabolism. It is administered via central venous line. It should not be delivered through the return port of the dialysis catheter as this can lead to recirculation of the calcium to the access limb and a need for higher citrate infusion rates.

An adequate systemic calcium level is needed to maintain the cardiac rhythm, cardiac muscle function and blood vessel tone. The infusion of calcium chloride must be titrated to maintain a **systemic ionized calcium of 1.0-1.3 mmol/L (or 1.0-1.2 may be ordered)**. A low systemic ionized calcium level can cause prolonged QT, cardiac arrest, Torsades de Pointes, decreased myocardial contractility and/or hypotension.

Any citrate that is not cleared via the dialysate is transported to the liver to be converted to bicarbonate. Citrate that is not metabolized by the liver will accumulate in the blood and chelate ionized calcium, lowering the systemic ionized calcium levels. The chelated ionized calcium is replaced by the calcium chloride infusion.

### **Citrate Toxicity**

Patient's with liver failure (which can include shock liver) or lactic acidosis may develop citrate toxicity. When the liver is unable to clear citrate effectively, the increased systemic citrate will combine with systemic ionized calcium to lower the ionized calcium level and increase the amount of calcium-citrate. The Total Calcium level (measured in the Core Lab) is the total of all calcium, including the ionized, protein bound and calcium-citrate forms.

**Total Calcium** = calcium bound to protein + ionized calcium + calcium-citrate complex

We don't have the ability to measure the amount of calcium-citrate in the blood. Instead, we look for a rise in the Total Calcium in the absence of a rise in the ionized calcium as an indication that calcium-citrate is accumulating.

An increase in the difference between the Total Calcium and Systemic Ionized Calcium (Total Calcium – Ionized Calcium) during citrate administration suggests citrate toxicity (this is known as an increased calcium gap). A Total Calcium/Ionized Calcium ratio (Total Calcium to Ionized Calcium Ratio) of > 2.5 suggests citrate toxicity.

Liver function tests, bilirubin and Total to Ionized Calcium ratios are measured daily to identify risk factors/signs of citrate toxicity. Escalating requirements for citrate and calcium chloride (particularly in a patient who has been stable at previous rates) is often a sign of developing toxicity. If the patient was previously receiving a stable citrate infusion rate and now needs more citrate to achieve the same post filter ionized calcium level, a better strategy is often to accept higher post filter ionized calcium targets (e.g., 0.35-0.45 or 0.45-0.55).

Other signs of citrate toxicity include metabolic acidosis with an increased Anion Gap (AG) (citrate is an anion) and hemodynamic instability. If suspected, citrate should be discontinued.

### **Blood Flow Rates**

Blood flow rates when using citrate are maintained at a steady rate. Changes to the blood flow rate will change the rate of citrate elimination at the filter. Strive to maintain a blood flow of 150 ml/min to a maximum of 200 ml/min (higher rate only if needed to prevent access alarms).

### **Electrolyte Abnormalities**

ACD-A Citrate contains 224 mmol/L of sodium, therefore, administration of citrate can cause hypernatremia.

Because citrate that is metabolized by the liver will be converted to bicarbonate, another potential problem is metabolic alkalosis.

The development of hypernatremia and/or metabolic alkalosis is reduced if dialysate fluid is administered (therefore we always run dialysis fluid). If dialysis fluid is administered, any increase in the serum sodium or bicarbonate levels should be removed because of lower concentrations of these electrolytes in the dialysate. Serum sodium > 150 mmol/L or serum bicarbonate (from electrolyte panel) > 36 mmol/L should be reported to nephrology.

The volume of the citrate is automatically removed because it is administered via the PBP (the citrate becomes a form of predilution hemofiltration). The Calcium Chloride volume is infused outside of the Prismaflex™ system, therefore, it is included in the IV intake.

### **Dialysate:**

To reduce the amount of citrate required to achieve post filter targets, we use dialysis fluid that does not contain any calcium (Prism0Cal).

Potassium must be added to the dialysate solution as Prism0Cal contains **ZERO POTASSIUM**.

## Hemofiltration (AKA Replacement fluid):

Because the PBP is used for the delivery of citrate, the only pump available to administer any hemofiltration solution is the replacement pump.

Because we must always run some replacement fluid POST filter to prevent clotting in the deaeration chamber (known as post dilution hemofiltration), we run all of our replacement fluid on the replacement pump as POST replacement. We generally maintain 1 Litre/hour of post filter replacement.

To reduce the chance of error when hanging solutions, we strive to use the same solution for both replacement and dialysis. This may need to be changed if hypernatremia/alkalosis develops.

Remember that anything running on the PBP is actually PRE dilution hemofiltration. Whatever rate the citrate is running at, an equal volume of fluid will be removed at the filter (e.g., the citrate is running at 300 ml per hour, therefore, an extra 300 ml per hour of effluent will be removed at the filter). You do not need to add the citrate volume when calculating intake and output.

## SAFETY TIPS

1. If the patient has suspected HITT or heparin allergy, do not prime the filter with heparin. If citrate is being used in a patient who cannot be systemically anticoagulated due to risk for bleeding, but does not have HITT or heparin allergy, the filter can be primed with heparin. The second priming bag should be plain normal saline without heparin.
2. Before starting citrate, measure the systemic (arterial line) ionized calcium and give a bolus per protocol so that we are starting with the patient already normalized.
3. Initiate the calcium chloride infusion 15 minutes before starting the treatment to reduce the chance of hypocalcemia.
4. We always run dialysate to reduce the chance of hypernatremia or metabolic alkalosis and our standard rate is 1L/hour.
5. We use CALCIUM FREE dialysate solution called PrismOCal to reduce the citrate requirements.
6. **PrismOCal is also Potassium free; it is essential that we add potassium to every bag of dialysate fluid.** If a patient is dialyzed against a dialysate with 0 potassium, they could quickly become profoundly hypokalemic. We do not administer dialysate in CCTC with less than 2 mmol/L of potassium.
7. It is not necessary to add potassium to the replacement fluid IF YOU ARE ADDING IT TO THE DIALYSATE. It is not wrong to add potassium to the replacement fluid and when our CRRT orders go live into HUGO, we will be adding potassium to both replacement and dialysate bags (primarily to reduce the chance of error). If the patient's potassium is hard to maintain or you feel more comfortable adding it to the replacement, potassium can be added to the replacement as well.
8. Maintain a steady blood flow rate whenever possible to minimize changes to the citrate and calcium chloride requirements.

## SUMMARY OF IMPORTANT POINTS

- Always consider hypocalcemia if a patient suddenly drops their heart rate or blood pressure. Keep an ampule of calcium chloride at the bedside in case of emergency.
- Remember, the patient must always have potassium added to the dialysate bag. We never run any dialysate solution with less than 2 mmol/L potassium in CCTC.
- Don't over correct post filter ionized calcium. If the patient begins to require higher doses of citrate, consult nephrology and consider reducing the post filter ionized calcium targets to 0.35-0.45 or 0.45-0.55 mmol/L.
- Strive to maintain blood flow at 150 ml/min
- Citrate Toxicity can develop with prolonged use, shock or liver impairment.

### Signs and symptoms of Citrate Toxicity:

- Increasing requirements for citrate and calcium chloride. This is called tachyphylaxis (or higher doses of a medication required to produce the same effect)
- Increased Total Calcium without an increase in the systemic ionized calcium level (or Total Calcium/Ionized Calcium ratio > 2.5.
- Sudden and unexpected hypotension, long QT, bradycardia/cardiac arrhythmia, decreased cardiac output
- Metabolic acidosis with increased anion gap
- Notify nephrology if Na > 150 mmol/L or Bicarb > 36 mmol/L (from electrolyte panel).
- Systemic ionized calcium levels > 1.3 may be harmful, therefore, avoid over correction.

## References

Link et al. (2012) Total-to-ionized calcium ratio predicts mortality in continuous renal replacement therapy with citrate anticoagulation in critically ill patients *Critical Care*, 16:R97 <http://ccforum.com/content/16/3/R97>

Davenport et al. (2009) Citrate anticoagulation for continuous renal replacement therapy (CRRT) in patients with acute kidney injury admitted to the intensive care unit. *September 25, 2: 439–447* <http://ckj.oxfordjournals.org/content/2/6/439.full.pdf+html>