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 PrisMax™ or PrismaFlex™ CRRT machine, citrate is administered via the Pre Blood Pump (PBP), entering the blood very close to the patient's access limb. This provides immediate anticoagulation of the blood before it reaches the filter. 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 low **post filter ionized calcium (initially 0.36-0.45 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.

Any citrate that is not cleared via the dialysate is transported to the liver where most of the citrate is converted to bicarbonate. A small amount can be metabolized in the muscles and kidney. Citrate that is not dialyzed or metabolized to bicarbonate will accumulate in the blood and chelate ionized calcium in the systemic circuit, lowering the systemic ionized calcium levels. The chelated systemic ionized calcium is replaced by the calcium chloride infusion.

Calcium chloride is titrated to achieve a steady state between the citrate that enters the systemic circulation and the rate of hepatic citrate metabolism, and to replace the calcium lost through the dialysis filter. It is administered via a central venous line that is separate from the dialysis circuit. 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.

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 need to escalate the calcium chloride infusion after initial stabilization may indicate citrate toxicity induced hypocalcemia.

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 stable citrate infusion rates and now needs higher doses to maintain post filter ionized calcium targets, consider raising the target to (0.45-0.55 mmol/L) and rule out citrate toxicity.

Other signs of citrate toxicity include metabolic acidosis with an increased Anion Gap (AG) (citrate is an anion) and hemodynamic instability. Hypocalcemia induced bradycardia, QT prolongation or cardiac arrest may occur. If suspected, citrate should be discontinued and any systemic ionized calcium deficit corrected urgently.

Changes to the blood flow rate will change the rate of citrate elimination at the filter. Strive to maintain a steady blood flow rate/monitor the ionized calcium levels following any rate change. The target blood flow should be fixed at 150 ml/min (unless higher rates are required to manage access and return pressures.

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 with normal sodium and bicarbonate concentrations). If dialysis fluid is administered, any increase in the serum sodium or bicarbonate levels above the dialysate level should be removed by diffusion. Serum sodium > 150 mmol/L or serum bicarbonate (from electrolyte panel) > 36 mmol/L should be reported to the physician.

The hourly citrate volume 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 PrisMax™ and PrismaFlex™ system, therefore, it must be included in the IV intake when calculated net fluid balance.

Because the citrate is administered on the PBP pump, the citrate infusion will automatically stop anytime the machine is stopped for bag changes or due to an alarm that stops the blood pump. This is an important safety feature that prevents inadvertent systemic citrate administration.

Dialysate:

To reduce the amount of citrate required to achieve post filter targets, we use dialysis fluid that does not contain any calcium (Prism0CAL). We generally use 1 L of dialysis fluid per hour.

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

Hemofiltration (AKA Replacement fluid):

Since the PBP is used for the delivery of citrate, the only pump available for hemofiltration solution is the replacement pump. Because we must always run some replacement fluid POST filter to prevent clotting in the deaeration chamber, all fluids that are administered via the replacement pump are delivered as POST dilution replacement.

Post dilution does improve clearance by concentrating the blood in the filter to enhance diffusion gradients. This clearance advantage does not usually impact treatment when we predominantly use predilution fluids for our No Anticoagulation or Heparin therapies. The trade-off off when administering post dilution replacement is an increased potential for premature filter clotting due to hemoconcentration. Filter clotting is not usually a concern when using citrate anticoagulation.

Calcium containing solutions could be used for the post filter replacement fluid, which might reduce the calcium chloride infusion requirements. There is a theoretical risk that this might increase the risk for clotting in the return limb of the catheter. We have chosen to use PrismOCAL for both the dialysate and post dilution replacement fluids in order to reduce the risk for error by mixing up the bags.

Rarely, the post replacement fluid may need to be modified with prolonged citrate use to manage hypernatremia or alkalosis if it develops. Although we do not keep a supply of CRRT solutions with lower bicarb concentration in CCTC due to infrequent use, PrismOCAL B 22 may be ordered through HMMS (Calcium, glucose and potassium free with a bicarbonate of 22 mmol/L).

Glucose Consideration

PrismOCAL does not contain glucose. Patients in CCTC will usually be receiving another source of glucose (IV or enteral). Careful blood sugar and insulin monitoring is required when starting or stopping CRRT using PrismOCAL.

For insulin dependent diabetics, use of PrismOCAL may cause dilution and clearance of blood glucose with a misleading normoglycemia. Consider the possibility of DKA if an unexplained anion gap metabolic acidosis develops despite normoglycemia.

Summary Administration

1. If the patient has suspected HITT or heparin allergy, do not prime the filter with heparin.
   If citrate is being administered with an ST 150 filter or larger, prime the filter with heparin (the patient will not receive a heparin bolus). An ST 150 requires 2 litres of priming solution. The first litre of priming solution contains 5,000 units of heparin. The heparin will bind to the layers in the filter. The second litre of saline removes any heparin solution from the circuit.

   Smaller filters that require only a single litre of priming solution should not be primed with heparin if systemic anticoagulation is contraindicated (not generally used in adults)

2. Before starting citrate, measure the systemic (arterial line) ionized calcium and give a bolus of calcium per protocol to begin treatment from a normal baseline.

3. Initiate the calcium chloride infusion 15 minutes before starting the treatment to reduce the chance of hypocalcemia.

4. We run dialysate to reduce the chance of hypernatremia or metabolic alkalosis and our standard rate is 1L/hour.

5. Citrate is always administered on the PBP. This ensures the infusion stops if the pumps are paused, preventing accidental systemic administration of citrate.

6. We use a CALCIUM FREE dialysate solution called PrismOCal to reduce the citrate requirements.

7. We use PrismOCAL on the replacement pump to reduce the risk of error. It is run as post dilution replacement.

8. **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.

9. Maintain a steady blood flow rate whenever possible to minimize changes to the citrate and calcium chloride requirements. The goal for the blood flow is a fixed 150 ml/min.

10. Monitor signs of citrate toxicity and treat low systemic ionized calcium quickly. Risk for toxicity increases with liver failure, shock and low flow states and prolonged use.

11. Don't over correct post filter ionized calcium; respond to trends versus a small rise in ionized calcium above target. If the patient begins to require higher doses of citrate, consider increasing the post filter target to 0.45-0.55 mmol/L.

12. Citrate Toxicity can develop with prolonged use, shock or liver impairment.

13. **Treat Quickly if Citrate Toxicity Suspected:**

    - Stop citrate
    - Increase dialysis flow rate to clear citrate
    - Monitor and treat systemic hypocalcemia quickly

14. **Signs and symptoms of Citrate Toxicity:**

    - Low systemic ionized calcium and escalating requirements for calcium chloride due to binding of ionized calcium to the surplus citrate.

- Increasing requirements for citrate along with increasing calcium chloride requirements.
- 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 (due to systemic hypocalcemia)
- Metabolic acidosis with increased anion gap

References

Link et al. (2012) Total-to-ionized calcium ratio predicts mortality in continuous renal replacement therapy with citrate anticoagulation in critically ill patientsCritical 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

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