Worcestershire Acute Hospitals NHS Trust

Protocol for Citrate Anticoagulation for Renal Replacement Therapy in Intensive Care

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Key Amendments

Date	Amendment	Approved by
14th October 2019	Document approved by Critical Care Forum and Medicines Safety Committee	Critical Care Forum and MSC

1. Introduction

Overview

The use of extra-corporeal circuits, such as those used for renal replacement therapy, frequently require the use of anticoagulation to prevent clotting in the circuit and thus prolong filter life and reduce the amount of patient blood lost due to discarded circuits.

Historically heparin has been the drug of choice for anticoagulation in these patients which, although relatively simple to administer and titrate, has a number of drawbacks. These include the need for systemic anticoagulation (i.e. anticoagulation of the patient as well as the circuit) and therefore the risk of bleeding. Systemic anticoagulation may be contraindicated in those who have recently undergone surgical intervention, or have other haemorrhage risks such as those who have had a recent intracerebral bleed. Heparin is ineffective in patients with anti-Thrombin III deficiency and it can be difficult to monitor efficacy in patients with coagulopathy. Furthermore, heparin induced thrombocytopenia is not infrequently suspected in the critical care population and this can preclude the use of heparin whilst awaiting confirmatory tests.

Citrate is used for anticoagulation in an increasing number of units both around the UK and internationally and has been show to prolong circuit life and reduce patient blood transfusion requirements relative to heparinisation. Citrate is used as regional anticoagulation which means that the anticoagulation effect can be reversed before blood is returned to the patient. This means it can be used in situations where heparin may previously have been contraindicated.

The use of citrate as an anticoagulant also has some disadvantages. It is a more complex system to set up and monitor, and requires the use of different dialysate and replacement fluids. It also has the potential to cause metabolic disturbances and hypocalcaemia although these can be monitored and managed.

Summary
Summary characteristics

- Ionised calcium is the active form of calcium in the blood and is a key requirement of the clotting process.
- Citrate binds to ionised calcium to prevent clotting.
- Using the pre-blood pump of the Prismaflex™ allows citrate to be added to the patient's blood as soon as it enters the dialysis line.
- The citrate chelates the calcium (and other divalent cations, principally Mg^{2+}) to result in a calcium-citrate (or other cation-citrate) complex.
- Adjustment of the citrate infusion is made to maintain a very low ionised calcium level in the blood entering the filter. This is measured as a post-filter ionised calcium level as this is much easier in practice than sampling pre-filter.
- The calcium-citrate complexes are principally removed in the dialysis fluid and the calcium is replaced by a systemic calcium infusion to maintain normal ionised calcium levels in the patient.
- The calcium replacement is given via a central line and not via the dialysis line to prevent recirculation and thus the need for higher doses of citrate.
- The small amount of citrate and calcium-citrate complex that returns to the patient is metabolised by the liver and is converted to bicarbonate.
- If more citrate returns to the patient than the liver can metabolise (this is fairly rare) then it will build up in the circulation, causing chelation of the systemic calcium and a metabolic acidosis. This can be monitored and managed.
- Maintenance of the systemic ionised calcium between 1.0 and 1.3 is paramount to prevent hypocalcaemia.
- Hypocalcaemia can lead to cardiac arrhythmias, hypotension, and cardiac arrest.
- Monitoring for citrate toxicity (using the total calcium:ionised calcium ratio) and maintenance of normal electrolyte levels (ionised calcium, magnesium) are fundamental to the successful and safe use of citrate anticoagulation.

Background Information

Citrate

- Citrate refers to the chemical compound citric acid and its salts. These citrate molecules chelate (bind to) calcium and render it inactive in the blood.
- Calcium is a fundamental component of the human clotting process and inactivation by the addition of citrate results in profound anticoagulation.
- Citrate is added to the patient's blood before it passes through the extra-corporeal circuit thus preventing clotting.
- To avoid full anticoagulation of the patient additional calcium must be administered to reverse the systemic anticoagulation effect.
- Some of the citrate molecules with their bound calcium are filtered out during renal replacement therapy; the rest is returned to the patient where it is metabolised by the liver to produce bicarbonate and release its calcium back into the blood. Consequently, severe liver failure is one of the contraindications to use of citrate.
- Dialysate and pre-dilution fluids should be calcium free so that they do not reverse the effects of the citrate before the blood has returned to the patient.
- Citrate can also bind magnesium, so serum magnesium levels must be monitored.

3.2 Calcium

- Knowledge of calcium physiology is important to understanding the monitoring and replacement of body calcium levels.
- As well as its involvement in the clotting system calcium is also a vital component of many other physiological systems. These include cardiac function, blood pressure regulation, nervous system control and bone and muscle function. Maintenance of a normal blood calcium level when using citrate is paramount to preserve the activity of these vital body systems.
- The majority of calcium in the human body is found in bone. Calcium can be absorbed and resorbed from bone under hormonal control; however, it is only the calcium in the blood which we can measure using blood tests and which we monitor during citrate anticoagulation.
- Calcium in the blood is found as 'free' ionised calcium, calcium bound to blood proteins (predominantly albumin), and calcium bound to other complexes (including citrate) in the blood. These three fractions make up the total calcium as measured on a laboratory blood test.

- Although there is equilibrium between these three fractions it is the ionised calcium which takes part in clotting and which the citrate will bind to.
- Ionised calcium is measured on a near patient testing blood gas analyser.

3.3 Citrate Toxicity

- Patients with liver failure may be unable to metabolise the citrate-calcium complexes resulting in a rise in the plasma citrate level.
- As citrate is an anion (negatively charged), accumulation can lead to a raised anion gap metabolic acidosis.
- A rise in the total calcium in the absence of a rise in the ionized calcium as an indication that the calcium-citrate complex is accumulating.
- Measuring the total calcium to ionised calcium ratio can help identify accumulation of citrate.
- A total calcium:ionised calcium ratio of > 2.5 suggests citrate toxicity.
- Because citrate returning to the patient is metabolised to bicarbonate by the liver, some patients may develop a metabolic alkalosis as each citrate molecule produces three bicarbonate molecules.
- Because the citrate infusion fluid contains a moderately high dose of sodium, hypernatremia may develop.
- Using dialysate fluid (i.e. CVVHD/CVVHDF) can reduce the risk of hypernatremia and metabolic alkalosis.

3.4 Calcium Replacement

- Calcium replacement is administered via a central venous line. It should not be delivered through the return port of the renal replacement therapy catheter as this can lead to recirculation of the calcium and a need for higher citrate infusion rates.
- Calcium should <u>always</u> be replaced via a central vein and not peripherally as it is a potent cause of extravasation injury.
- Normal systemic ionised calcium as measured on a blood gas analyser should be between 1.0 and 1.3mmol/L
- The ionised calcium within the renal replacement circuit should be kept <0.35mmol/L to ensure adequate anticoagulation.

3.5 Indications

- Regional citrate will be the default anticoagulation for patients requiring renal replacement therapy within the intensive care, unless there is a contraindication or senior medical staff have specified otherwise.

3.6 Contraindications

- Severe liver failure – patients with severe liver failure may be unable to metabolise citrate and thus have a high risk of developing citrate toxicity.
- Citrate intolerance or allergy.
- Patients with an ionised calcium <0.8 – this must be corrected to >1.0 prior to initiation of citrate.

4 Preparation

4.1 Equipment

Table 1 lists the equipment required in order to set up the Prismaflex™ for citrate anticoagulation:

CRRT Prescription	2 x 1L 0.9% sodium chloride
1 x Prismaflex™ ST150 filter	2 x 21g needles for sampling
1 x 5L Prism0cal	1 x 50ml BD syringe
1 x 5L PrismaSol	3 x 10ml ampoules of Calcium Chloride 10%
1 x 5L bag of Prismocitrate 18/0	1 x Prismaflex™ circuit

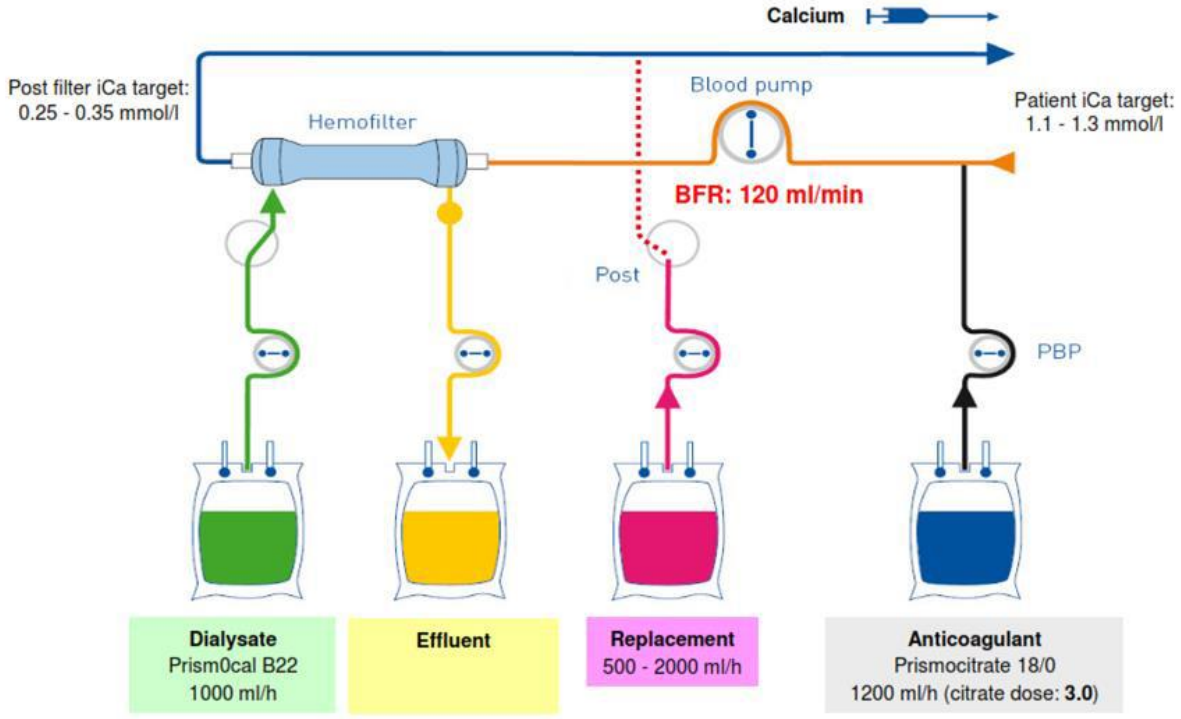
Table 1 - Equipment Required for Set-Up

4.2 Set-Up

- Prepare the calcium replacement by drawing up 30mls of 10% Calcium Chloride (30mmol) into a 50ml syringe and make up to 50mls using 0.9% sodium chloride giving a final concentration of 0.6mmol/ml.
- Set up the Prismaflex™ machine using the “New Patient” setting.
- Select CCVHDF protocol.

- Choose “Citrate-Calcium via Prismaflex™ syringe pump” as the anticoagulation method.
- Ensure that the correct fluid bags are chosen and placed on the correct scales. This should be checked by another member of staff also trained in providing citrate anticoagulation.
    - Prismocitrate 18/0 on the white scales connected to the pre-blood pump.
    - Prism0cal B22 on the green scales connected to the dialysate circuit.
    - PrismaSol on the purple scales connected to the replacement fluid circuit.
- Connect the calcium replacement syringe previously prepared to the Prismaflex™ syringe pump.
- Prime the circuit using 0.9% sodium chloride. There is no need to prime the circuit with heparin unless the patient is already on a heparin infusion (to avoid a drop in systemic heparin levels due to adsorption of heparin onto the filter surface) or is expected to be on a heparin infusion during RRT, for example if citrate is contraindicated.
    - If heparin priming is to be used 5000units Heparin should be added to the first 1000ml bag of 0.9% sodium chloride, subsequent bags do not need the addition of heparin.
    - The filters circuits have a coating of polyethylimine which has a positive charge and therefore heparin sticks to the filter. Priming with heparin coats the filter so that any systemic heparin does not bind to the filter and thus it is easier to achieve the target APTT.

Set Up Illustration (With Example Flow Rates)



Initiation of RRT
4.1 Blood Flow Rate

During setup the Prismaflex™ will ask you to set the "blood flow rate", "dialysate" and "replacement" rates. This should be done based on the patient's weight using the parameters demonstrated in Table 2:

Weight (kg)	Blood Flow (ml/min)	Dialysate (ml/hr)	Replacement post-filter (ml/hr)	Treatment dose obtained (ml/kg/hr)
<= 50	100	1000	200	37
51 -60	110	1100	400	37
61- 70	120	1200	500	35
71 - 80	130	1300	500	33
81 - 90	140	1400	500	31
91 - 100	150	1500	600	31
101 - 110	160	1600	700	30
111 - 120	170	1700	800	30
>= 121	180	1800	1000	30

Table 2 - Initial Flow Settings

5.2 Calcium Replacement

- When prompted the starting citrate dose should be set to 3mmol/L
- The initial calcium compensation should be set based on Table 3 and is dictated by the patient's initial ionised calcium from a blood gas sample.
- Patients with an ionised calcium below 1.0mmol/L should receive 10mls calcium chloride 10% over 30mins via a central vein before initiation of citrate therapy.

Patient ionised calcium (mmol/L)	**Starting calcium compensation (%)**
Less than 1.00	Give calcium replacement and start at 110%
1.00 – 1.11	110%
1.12 – 1.30	100%
Greater than 1.30	90%

Table 3 - Initial Calcium Compensation

Monitoring

5.1 Overview

Monitoring will consist of three elements

1. Patient's total and ionised calcium levels
2. Filter ionised calcium level
3. Liver function, magnesium and phosphate levels

6.2 Frequency

- The frequency of testing is shown in Table 4.
- Steady state sampling can commence once there has been no changes required to citrate or calcium doses for two consecutive hours.
- The total calcium is not corrected for albumin when used to calculate the total calcium:ionised calcium ratio.

Sample	Initially	Steady State
Filter ionised calcium	Hourly	6 hourly
Patient ionised calcium	Hourly	6 hourly
Total calcium (uncorrected)	6 hours after starting	Daily
Magnesium	-	Daily
Phosphate	-	Daily
Liver function tests	-	Daily

Table 4 - Sampling Frequency

6.3 Adjustments

Based on the sampling from the patient use Table 5 to make adjustments to the dose of the citrate and calcium

		Filter ionised calcium		
		< 0.25	**0.25 – 0.5**	**> 0.5**
Patient ionised calcium	**<1.0**	Citrate dose decreased by 0.5mmol/L	Calcium compensation increased by 10%	Citrate dose increased by 0.5mmol/L **and** Calcium compensation increased by 10%
	1.0 – 1.3	Citrate dose decreased by 0.5mmol/L	No change required	Citrate dose increased by 0.5mmol/L
	>1.3	Calcium compensation decreased by 10% **and** citrate dose decreased by 0.5mmol/L	Calcium compensation decreased by 10%	Calcium compensation decreased by 10%

Table 5 - Treatment Adjustment Algorithm

6.4 Restarting Patients on Citrate

- Restart using the citrate dose and calcium replacement rate from when treatment last finished.

5.1 Total Calcium:Ionised Calcium Ratio

- Daily checks of the total calcium:ionised calcium ratio must be performed – this is to monitor for citrate toxicity.
- This will require a laboratory calcium, and a blood gas calcium to be taken at the same time.

$$\frac{\boldsymbol{Total\ calcium\ (uncorrected)}}{\boldsymbol{Patient\ ionised\ calcium}} = \boldsymbol{total\ calcium{:}\ ionised\ calcium\ ratio}$$

Formula to calculate total calcium:ionised calcium ratio

- The ratio should be <2.5, if this is the case then repeat the calculation again in 24 hours.

- If the ratio is >2.5 this can be a sign of citrate toxicity and expert help should be sought from a consultant or senior registrar. There are two steps that may be taken initially. These are shown in Table 6.

Ratio	Action
<2.5	Normal. Repeat ratio in 24 hours
>2.5	Seek consultant or senior registrar support. See Section 5.1 for management of citrate toxicity

Table 6 - Total Calcium:Ionised Calcium Monitoring

6 Important Points

7.1 Patient Ionised Calcium

- If at any stage the patient's systemic ionised calcium is <0.7mmol/L administer 10mls calcium chloride 10% to prevent physiological instability. This should be done as a priority and should be given via a central line as a slow bolus over 10minutes.
- A drop in the patient's heart rate or blood pressure should always prompt assessment for hypocalcaemia and emergency calcium replacement if low.

5.1 Citrate Toxicity

- A total calcium:ionised calcium ratio >2.5, worsening metabolic acidosis without alternative explanation (pH <7.35 or BE <-4) or rising anion gap should prompt consideration of citrate toxicity.
- If citrate toxicity is suspected senior medical advice should be sought.
- A total calcium:ionised calcium ratio should be measured.
- Consider the cause for citrate build up from administration to breakdown. Potential causes include:
    - Excess citrate administration via RRT
    - Administration of exogenous additional citrate such as with blood transfusions
    - Developing or worsening liver dysfunction
    - Worsening hypoperfusion and consequently less citrate metabolism by muscles
- Citrate toxicity should be managed in a step wise fashion

- Adjust the filter ionised calcium target to 0.4-0.5mmol/L (aiming to ride the higher end of the target range) by reducing the citrate dose in 0.2mmol increments. Check a filter ionised calcium every 30 minute until the new 0.4-0.5 mmol/L target achieved. This may mean that filter life and RRT clearance are reduced.
- Remeasure the total calcium:ionised calcium ratio once the filter ionised calcium target of 0.4-0.5 mmol/L is achieved.

- If the total calcium:ionised calcium ratio remains >2.5 despite the above measures consider any of the following actions:
  - Double baseline dialysate flow (to increase citrate removal)
  - Reduce blood pump speed by 10ml/min (this will reduce the citrate dose administered at the expense of overall filtration dose).
  - Stop citrate and use alternative anticoagulant or no anticoagulant.

5.2 Calcium Replacement

- If calcium replacement exceeds 150% then citrate toxicity should be excluded by checking a total calcium:ionised calcium ratio. If >2.5 inform medical staff (refer to 7.2)

8. Troubleshooting

8.1 Increasing Clearance

- To increase the clearance of solute the replacement fluid dose can be increased or settings can be adjusted to the next highest weight category as shown in Table 2. For example, if the patient weighs 84kg, use settings for the 91-100kg category.

8.2 Low bicarbonate

- If bicarbonate is consistently low the amount of citrate reaching the patient and thus metabolised to bicarbonate can be increased. This can be achieved either through reducing the dialysate dose or increasing the blood flow rate (and hence the citrate dose). Administration of systemic bicarbonate may also be considered.
- Ensure that the total calcium:ionised calcium ratio is <2.5 to exclude citrate toxicity before increasing the citrate dose received by the patient.

8.3 Metabolic Acidosis

- Patients in renal failure commonly have a metabolic acidosis as part of their disease process; it is expected that after initiation of RRT and treatment of the cause of the renal failure that any pre-existing metabolic acidosis should improve.
- Worsening metabolic acidosis whist on RRT should raise concern about citrate toxicity development (see Section 5.1.)

8.4 Metabolic Alkalosis

- Development of a metabolic alkalosis occurs if the patient is metabolising excess citrate as one citrate molecule is broken down into 3 bicarbonate molecules.
- Management may involve either a reduction in the citrate dose (by reducing the blood pump speed in 10mls/min increments) or increasing clearance by doubling the baseline dialysate flow rate.

This key document has been circulated to the chair(s) of the following committee's / groups for comments;

Committee
ICU Forum
Critical care and Anaesthetics Clinical Governance Committee
SCSD governance committee
Medicines Safety Commitee

Supporting Document 1 - Equality Impact Assessment Tool

To be completed by the key document author and attached to key document when submitted to the appropriate committee for consideration and approval.

		Yes/No	Comments
1.	**Does the policy/guidance affect one group less or more favourably than another on the basis of:**		
	Race	No	
	Ethnic origins (including gypsies and travellers)	No	
	Nationality	No	
	Gender	No	
	Culture	No	
	Religion or belief	No	
	Sexual orientation including lesbian, gay and bisexual people	No	
	Age	No	
2.	**Is there any evidence that some groups are affected differently?**	No	
3.	**If you have identified potential discrimination, are any exceptions valid, legal and/or justifiable?**	No	
4.	**Is the impact of the policy/guidance likely to be negative?**	No	
5.	**If so can the impact be avoided?**	N/A	
6.	**What alternatives are there to achieving the policy/guidance without the impact?**	N/A	
7.	**Can we reduce the impact by taking different action?**	N/A	

If you have identified a potential discriminatory impact of this key document, please refer it to Human Resources, together with any suggestions as to the action required to avoid/reduce this impact.

For advice in respect of answering the above questions, please contact Human Resources.

Supporting Document 2 – Financial Impact Assessment

To be completed by the key document author and attached to key document when submitted to the appropriate committee for consideration and approval.

	Title of document:	**Yes/No**
1.	Does the implementation of this document require any additional Capital resources	
2.	Does the implementation of this document require additional revenue	
3.	Does the implementation of this document require additional manpower	No
4.	Does the implementation of this document release any manpower costs through a change in practice	No
5.	Are there additional staff training costs associated with implementing this document which cannot be delivered through current training programmes or allocated training times for staff	No
	Other comments:	

If the response to any of the above is yes, please complete a business case and which is signed by your Finance Manager and Directorate Manager for consideration by the Accountable Director before progressing to the relevant committee for approval