Bradford Teaching Hospitals NHS
NHS Foundation Trust

Protocol for Continuous Renal Replacement Therapy using Regional Citrate Anticoagulation

ICU USE ONLY

Author	Tom Lawton, Consultant ICU
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Introduction

Citrate is the preferred method of anticoagulation for Continuous Renal Replacement Therapy (CRRT) at BRI and should be used for the majority of patients. The machines used (Gambro Prismaflex) are the same as for heparin, as are the filter sets and the mode of CRRT (haemodiafiltration). The fluids and software are different.

Citrate works by chelating (binding to) calcium in the blood, this renders the clotting cascade ineffective and consequently allows effective filtration. Some of the citrate-calcium complex is removed by the filter and the rest is cleared by the liver. Calcium is then replaced after the blood has passed through the filter, allowing normal coagulation to occur.

The citrate is given as pre-dilution (Prismocitrate 18/0), the dialysate is Prism0cal B22 and then post dilution replacement is Prismasol 4. Calcium chloride is given separately as replacement for the lost calcium.

There are a number of anticipated advantages to this system. Filter life is prolonged, access issues less frequent and nursing workload reduced. Haemorrhage risk is less than with heparin and the Heparin Induced Thrombocytopenia risk is avoided.

Due to the regional nature of the anticoagulation the CRRT may continue to run whilst procedures such as percutaneous tracheostomy are undertaken. Separate systemic thromboprophylaxis should be prescribed as per normal protocols.

The major potential complications are hypocalcaemia and citrate accumulation.

Hypocalcaemia is common but rarely symptomatic. The protocol guides alteration of the calcium replacement infusion based upon the patients ionized calcium (from an arterial line, central line or peripheral stab) and the post filter ionized calcium taken from the blue port.

Citrate accumulation is more serious but uncommon, it results from failure of the patients liver to clear the infused citrate and is monitored with the T:I ratio (total to ionised calcium). The protocol below details its management.

This protocol is adapted from information provided by Gambro, Eastbourne ITU, and a local modification of the Kalmar protocol.

Before starting treatment

- Check the daily blood results before the start of treatment to include:
  - Adjusted Calcium**,** Magnesium and Potassium levels
  - Ensure a recent arterial blood gas includes a Calcium (ionised calcium)
  - Haematocrit
- Calculate total:ionized (T:I) calcium ratio using methods described later, if greater than 2.5 discuss with medical staff.
- **Correct ionized hypocalcaemia** – near normal starting values will make achieving stability much quicker and reduce number of blood tests needed.

Cautions

NB Citrate can still be used in these patients but close attention should be paid to calcium, pH, and the T:I ratio.

Increased risk of citrate accumulation

- Severe lactic acidosis/cardiogenic shock
- Severe liver failure
- Ethylene glycol poisoning
- Amphetamine/MDMA poisoning
- Cyanide poisoning
- Mitochondrial cytopathy
- HIV medication

Increased risk of hypocalcaemia

- Rhabdomyolysis (also increased risk of muscle damage in survivors)
- Amphetamine/MDMA poisoning
- Pancreatitis
- Tumour lysis syndrome
- Toxic shock

Equipment needed

- 1 Kit Prismaflex ST150
- 1 CA250 Calcium line
- 1 50ml Luer lock syringe
- Y connector
- 1 bag of 5L **PRISMOCITRATE 18/0** (citrate used as pre-dilution)
- 1 bag of 5L **PRISM0CAL B22** (dialysate)
- 1 bag or 5L **PRISMASOL 4** for replacement (post dilution)
- 0.9% Sodium Chloride (priming solution) – 2000mls for ST150
- Calcium Chloride 30mmol to 50mls 0.9% Sodium Chloride (3 ampoules made up to 50ml with 20ml 0.9% sodium chloride)

Setting up and priming circuit

- Choose the option CVVHDF
- Choose Citrate –Calcium via Prismaflex Syringe Pump
- Follow the installation steps on the screen.
- Install **PRISMOCITRATE 18/0** on the white scale (PPB = Pre Blood Pump).
- Install **PRISM0CAL B22** on the green scale. (Dialysate).
- Install **PRISMASOL 4** on the purple scale (Replacement).
- Prime the circuit with 2L (ST150) of 0.9% Sodium Chloride (NO Heparin required)
- Install the CALCIUM Chloride syringe in the Prismaflex syringe pump

Starting parameters

MODE: CVVHDF
STARTING CITRATE DOSE IS 3.0 MMOLS/L/BLOOD

Flow rates: See Appendix

Patient fluid removal as required based on the patients fluid balance, consider this as the equivalent of the patients urine output.

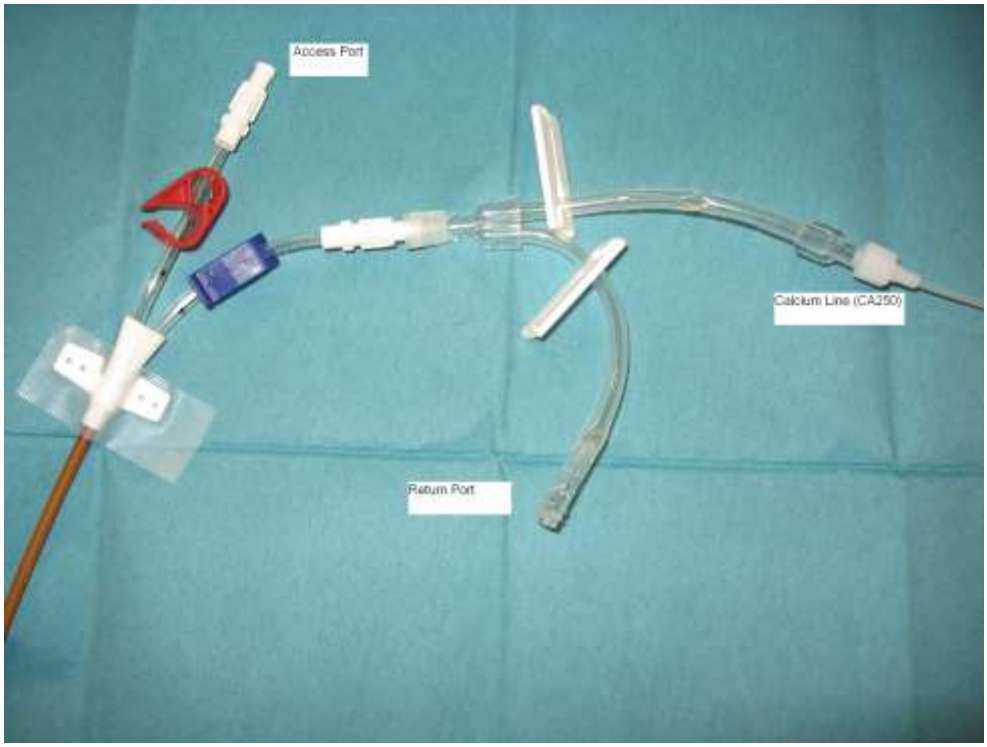
Haematocrit

This must be checked on an up to date arterial blood gas (or lab sample) and entered into the Prismaflex machine. Any change in haematocrit (i.e. if transfused or given large volumes of fluid) needs to be updated on the machine also. Changes in haematocrit effect the machine calculated citrate dosing.

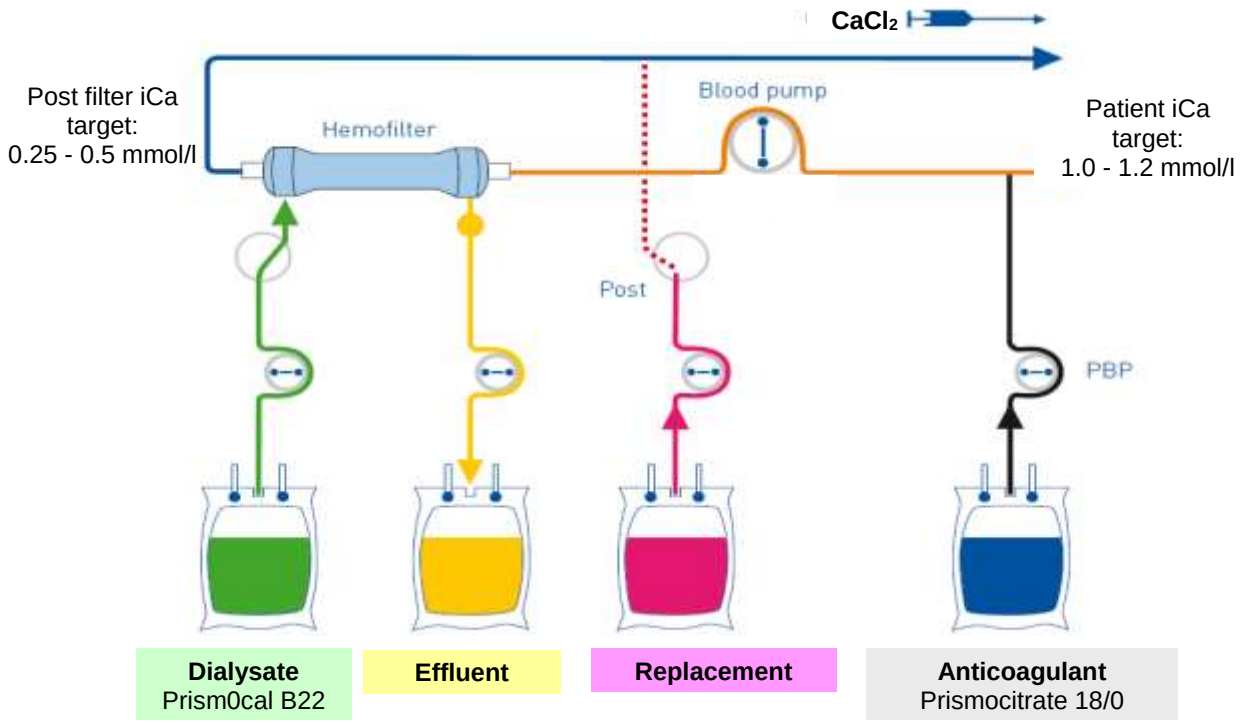
Connection

1. Connect access line to patient (red)
2. Connect Blue return line to the vacated port on the Y connector
3. Connect yellow line to effluent bag
4. Connect **CALCIUM** line to available port on the Y connector
5. Disconnect Y connector from priming bag spike and attach to patient
6. Tape calcium line to return line
7. Unclamp all lines

See photo & diagram for additional guidance.



Please note that Gambro advise connecting the Calcium line directly to the patient's central line, and the connection to a Y connector attached to the catheter is an unofficial procedure that has been found to have advantages. Taping the calcium line to the return line prevents inadvertent error if the return and access lines are switched (i.e. when troubleshooting access issues).



Treatment monitoring

Once treatment is initiated and blood flow established at one hour make two ionised Calcium checks (one from the blue port on the set and another from the patient's arterial line) and alter according to the table on the next page

Check post filter ionized calcium and patient calcium **hourly** until ideal values have been established then perform a check every **6 hours.**

If there are any changes in citrate dose or blood flow rate then patient and filter calcium must be rechecked in one hour.

In the event the patient does not have an arterial line the patient sample should be taken from a central venous catheter. If the patient has neither arterial or central line then a patient sample may be taken from the red port closest to the vascath, this is not ideal and may lead to abnormal values, an arterial line should be sited if feasible. The red port on the machine is not suitable for sampling. Sampling from a trilyse line is not appropriate as it may give abnormal values.

Increasing requirements for calcium compensation could indicate citrate accumulation and the calcium ratio should be checked. If the patient is hypocalcaemic before filtration it is not uncommon to transiently require 130-150% calcium compensation, this can be avoided by correcting calcium prior to initiating filtration.

		FILTER VALUES		
		Filter Ca^{2+} >0.50	**Filter Ca^{2+} 0.25 – 0.5**	**Filter Ca^{2+} <0.25**
PATIENT VALUES	**Patient Ca^{2+} <1.0**	Increase citrate dose by 0.5mmol/l Increase calcium compensation by 10% **If patient Ca^{2+} <0.8 then bolus 10ml Ca infusion**	Increase calcium compensation by 10% **If patient Ca^{2+} <0.8 then bolus 10ml Ca infusion**	Decrease citrate dose by 0.5mmol/l **If patient Ca^{2+} <0.8 then bolus 10ml Ca infusion**
	Patient Ca^{2+} 1.0 – 1.2	Increase citrate dose by 0.5mmol/l	**Normal Ideal Values**	Decrease citrate dose by 0.5mmol/l
	Patient Ca^{2+} > 1.2	Decrease calcium compensation by 10%	Decrease calcium compensation by 10%	Decrease calcium compensation by 10% Decrease citrate dose by 0.5mmol/l

If there are any changes in citrate dose or blood flow rate then patient and filter calcium must be rechecked in one hour.

Example 1 - patient ionised calcium 1.25, filter ionised calcium 0.35 = “Decrease calcium compensation by 10%”

Example 2 – patient ionised calcium 1.15, filter ionised calcium 0.22 = “Decrease citrate dose by 0.5mmol/l”

Calcium T:I Ratio Monitoring – Initial check after 6 hours

Divide patients total (uncorrected) calcium by the patient's ionised calcium: the T:I ratio.

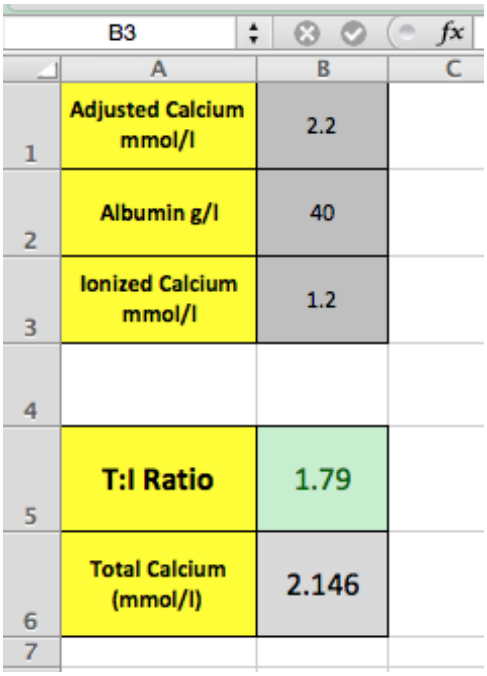
Method 1 (ideal):

Using **Total Calcium**.
This will become available electronically; at present it can be obtained by asking a biochemistry technician (phone 4076) – the pathology secretaries may be unable to access it.
Divide the **Total Calcium** by the **Ionised Calcium** (from the patient's latest ABG) using a calculator or the ICU spreadsheet (please be sure to you are using *Total* and not *Adjusted* Calcium). This gives the **T:I Ratio**.

Method 2 (backup)

Using **Adjusted Calcium**, when Total Calcium is unavailable.
The T:I calculator spreadsheet on the computers on ICU can reverse the correction applied by biochemistry to obtain a Total Calcium from an **Adjusted Calcium** and **Albumin**.
Input patient's up to date **Albumin**, **Adjusted Calcium** (from biochemistry) and **Ionised Calcium** (from latest ABG). The excel spreadsheet will then produce a value for both the **T:I Ratio** and the Total Calcium.

The manual calculation for Total Calcium is:
[Adjusted Calcium – ((43 – Albumin) x 0.018)]



T:I Ratio Value	Action
<2.5	**Check Daily**
>2.5	**Inform doctors** **Ensure that post filter calcium is 0.4 to 0.5 mmol/l if not decrease citrate dose until it is, then check calcium ratio again. If ratio is still above 2.5 and the post filter calcium is 0.4 – 0.5mmol/l then consider stopping citrate and use an alternative anticoagulant or no anticoagulant**

Monitoring timescale

MONITORING OF ANTICOAGULATION	Initially	And then
POST FILTER IONISED CALCIUM (Blood Gas from circuit) Target 0.25 to 0.50 mmol/L	Hourly until stable	6 Hourly
PATIENT SYSTEMIC IONISED BLOOD CALCIUM (Blood Gas from patient) Target 1.00 to 1.20 mmol/L	Hourly until stable	6 Hourly
PATIENT TOTAL CALCIUM (see above) Target 2.20 to 2.50 mmol/L		Daily
CALCIUM RATIO (Total Ca / Patient systemic ionised Ca) Target ratio <2.5	After 6 hours	Daily

Further monitoring

BLOOD GASES	REASON	Frequency
pH	To monitor acid base balance	4-6 hourly from blood gas or more frequently as clinically indicated
Base Excess/Bicarbonate	To monitor acid base balance	
Potassium	Monitoring for hypo or hyperkalaemia – replace if needed	
Glucose	Be aware there is no glucose in Prismocitrate 18/0	
Bicarbonate	One Citrate molecule converts to three bicarbonate molecules	

Daily monitoring

Magnesium	Urea
Phosphate	Haemoglobin
Haematocrit	Creatinine
Albumin	Sodium
Calcium (adjusted or total)	

Additional supplementation of magnesium and phosphate may be required. Please note above guidance regarding **haematocrit**, an up to date value must be inputted on the Prismaflex machine.

Complications and trouble shooting

Gambro 24hr helpline is 0808 100 3539.

Hypocalcaemia

This is a potential consequence of inadequate post filter replacement. Symptoms include paraesthesia, hypotension, arrhythmias and prolonged QT. Follow the above instructions by cross referencing the patient and filter Ca^{2+}.

Citrate Accumulation

This is a potential consequence of liver failure, lactic acidosis or CRRT management error. It causes an increased anion gap metabolic acidosis and refractory hypocalcaemia. Signs of this developing are:

- An otherwise unexplained worsening metabolic acidosis (with increased anion gap)
- Rising lactate
- Persistent ionised hypocalcaemia/increasing calcium replacement requirements
- TI ratio >2.5

Six hours after initiating CRRT and then daily you must check the total Ca:ionized Ca ratio. Also check this ratio at any time if clinically concerned. This described above.

If the T:I ratio is greater than 2.5:

- Ensure all settings are correct as per the charts above
- Ensure post filter Ca is 0.4-0.5 mmol/l by altering the citrate dose (i.e. minimal possible citrate dose)
- Check liver function and lactate, has one of the conditions listed above been missed?
- Notify the senior medical staff
- If this fails to correct the ratio and/or acidosis and hypocalcaemia then halt citrate anticoagulation. Either switch to heparin or use no anticoagulation.

Electrolyte disturbances

Sodium, magnesium, phosphate and potassium levels must all be monitored and replaced/controlled as needed. The replacement fluid does contain some electrolytes but additional supplementation may be required, particularly phosphate.

Inadequate clearance

Failure to clear acidosis, urea, creatinine or potassium can potentially be corrected by moving up the treatment chart by a weight level (i.e. 70kg patient treated with the settings for a 80kg patient). This may also be indicated where clearance of large molecules (such as myoglobin in rhabdomyolysis) is required or in poisoning and overdose cases. If treating the patient based on an altered weight please document on the chart as the “treatment weight”.

Excessive clearance can be managed by using a treatment weight that is less than actual body weight.

Metabolic acidosis/alkalosis

Due to citrate's conversion to bicarbonate there are high levels of bicarbonate delivered by the citrate solution (54 mmol/l) when compared to the dialysate solution (22 mmol/l). This allows the patients metabolic control to be altered with the CRRT.

By altering the ratio of citrate to dialysate you can alter the amount of bicarbonate being delivered to the patient. Relatively more citrate solution to dialysate means more delivered bicarbonate and will push the pH up. Conversely relatively less citrate to dialysate will push the pH down.

In the event of an acidosis other causes including citrate accumulation must be assessed.

If the patient develops a metabolic alkalosis on the CRRT (pH>7.45, BE >2) then increase the dialysate flow to the next level on the chart.

If the patient develops an increasing metabolic acidosis on the CRRT (pH<7.35, BE < -2) **and no other cause is found** then senior nursing or medical staff could consider reducing the dialysate flow to the next level on the chart. **A more straightforward solution, if clearance overall is poor, is to increase all treatment settings to the next weight band up** (i.e. treat a 70kg patient as if they are 80kg, see above). Separate bicarbonate supplementation can be considered – discuss with senior medical staff.

Appendix A - Fluid composition

All in mmol/l

Prismocitrate 18/0

- Citrate 18
- Sodium 140
- Chloride 86

Prism0cal B22

- Bicarbonate 22
- Lactate 3
- Sodium 140
- Potassium 4
- Magnesium 0.75
- Chloride 120.5
- Glucose 6.1

Prismasol 4

- Bicarbonate 32
- Lactate 3
- Sodium 140
- Calcium 1.75
- Potassium 4
- Magnesium 0.5
- Chloride 113.5
- Glucose 6.1

Appendix B – Bradford Flow Settings

High Dose (35ml/kg)

Weight	Blood flow	Dialysate	Replacement	Citrate (3mM)	Total (ml/hr)	Dose (ml/kg/hr)
50	*100*	*800*	*200*	1000	2000	40.0
60	*110*	*800*	*200*	1100	2100	35.0
70	*120*	*900*	*350*	1200	2450	35.0
80	*130*	*1000*	*500*	1300	2800	35.0
90	*140*	*1100*	*650*	1400	3150	35.0
100	*150*	*1200*	*800*	1500	3500	35.0
110	*160*	*1300*	*950*	1600	3850	35.0
120	*170*	*1400*	*1100*	1700	4200	35.0
130	*180*	*1500*	*1250*	1800	4550	35.0

Low Dose (25ml/kg)

Weight	Blood flow	Dialysate	Replacement	Citrate (3mM)	Total (ml/hr)	Dose (ml/kg/hr)
50	*80*	*500*	*200*	800	1500	30.0
60	*90*	*500*	*200*	900	1600	26.7
70	*100*	*550*	*200*	1000	1750	25.0
80	*110*	*600*	*300*	1100	2000	25.0
90	*120*	*650*	*400*	1200	2250	25.0
100	*130*	*700*	*500*	1300	2500	25.0
110	*140*	*750*	*600*	1400	2750	25.0
120	*150*	*800*	*700*	1500	3000	25.0
130	*160*	*850*	*800*	1600	3250	25.0

Low Dose should be the default protocol in stable patients or those for whom fluid management is the priority. Most patients should be on the low dose protocol after 24hrs to reduce the risk of hypophosphataemia/magnesaemia and excess drug clearance.

Use **High Dose** for patients who are starting the filter urgently (eg initial filtration in severe sepsis, rhabdomyolysis, hyperkalaemia) or have severe metabolic derangement which needs correcting rapidly.

If **Low Dose** is insufficient, increase to **High Dose**.

If **High Dose** is insufficient, either increase **Replacement** to give a total dose nearer 45ml/kg, or step up a weight band (nb this option increases citrate load).

Appendix C – Monitoring table

		FILTER VALUES		
		Filter Ca^{2+} >0.50	**Filter Ca^{2+} 0.25 – 0.5**	**Filter Ca^{2+} <0.25**
PATIENT VALUES	**Patient Ca^{2+} <1.0**	Increase citrate dose by 0.5mmol/l Increase calcium compensation by 10% **If patient Ca^{2+} <0.8 then bolus 10ml Ca infusion**	Increase calcium compensation by 10% **If patient Ca^{2+} <0.8 then bolus 10ml Ca infusion**	Decrease citrate dose by 0.5mmol/l **If patient Ca^{2+} <0.8 then bolus 10ml Ca infusion**
	Patient Ca^{2+} 1.0 – 1.2	Increase citrate dose by 0.5mmol/l	**Normal Ideal Values**	Decrease citrate dose by 0.5mmol/l
	Patient Ca^{2+} > 1.2	Decrease calcium compensation by 10%	Decrease calcium compensation by 10%	Decrease calcium compensation by 10% Decrease citrate dose by 0.5mmol/l

If there are any changes in citrate dose or blood flow rate then patient and filter calcium must be rechecked in one hour.