CITRATE ANTICOAGULATION FOR HAEMOFILTRATION

Background

Patients on continuous modes of renal replacement therapy require anticoagulation to prevent clotting of blood in the extracorporeal circuit.

Adequate anticoagulation prolongs circuit life but how long the membrane remains effective is debatable. Changing the filter every 48 hours is about right.

Citrate anticoagulation prolongs circuit life and causes less bleeding when compared with heparin.

Citrate Anticoagulation

Citrate acts by chelating calcium ions that are essential in the clotting cascade. It also chelates other divalent cations including magnesium and aluminium.

A plasma citrate concentration of about 5-6 mmol/L is required in order to reduce ionised calcium concentration to less than 0.6 mmol/L, which is required for anticoagulation. Adding approximately 2-3 mmol of citrate per litre of blood flowing through the filter usually achieves this.

Most of the added citrate returns to the patient and is metabolised rapidly by the liver, though there is a continuously slightly elevated systemic plasma citrate level which chelates some calcium in the systemic circulation. This can lead to a low systemic ionised calcium level even with normal total calcium. Also some chelated calcium is filtered, and as the substitution fluid contains no calcium there is a net loss of approx 2-3 mmol/kg/day in the filtrate.

In order to avoid systemic ionised hypocalcaemia, a separate infusion of calcium is required at a rate of approx. 2mmol/kg/day for a blood flow of 5ml/kg/min, and this is adjusted to maintain systemic plasma ionised calcium level of approx. 0.9-1.2 mmol/L.

To achieve optimal anticoagulation within the circuit using a citrate based substitution solution there must be a balance between circuit blood flow and substitution fluid flow rate. This ratio between citrate dose and circuit blood flow remains reasonably fixed allowing the prediction of what citrate dose (substitution flow rate) is needed for a particular blood flow rate.

A separate magnesium infusion may be necessary.

Citrate is metabolised to bicarbonate (3 molecules per molecule of citrate), mostly in the liver. A metabolic alkalosis therefore develops in protocols which add citrate separately (even when some of the citrate is as citric acid, eg acid-citrate dextrose), and hypernatraemia if the citrate is added as trisodium citrate. This is minimised if sodium citrate is an integral component of the substitution fluid, the citrate acting as the base instead of bicarbonate.

This only happens if the liver is able to metabolise the citrate load.
PROTOCOL

**NB: The circuit should be primed with 0.9% Saline**

*Relative Contraindications*

Citrate anticoagulation may NOT be an option for:

- Patients with severe **hepatic dysfunction**.
- Patients with “**Citrate lock**”, where citrate has accumulated during citrate anticoagulation.

These patients will need heparinisation as per the standard policy.

- Patients with **coagulopathy** (ACT >200 sec, or APTT > twice normal) MAY have neither heparin nor citrate, and bicarbonate-based substitution fluid is used.

*Substitution Fluid*

Made commercially in 5 Litre bags by Baxter/Edwards Life Sciences.

Be careful to distinguish between the 5 Litre bags containing citrate and those that are lactate free. Composition cannot be adjusted, except for the addition of Potassium Chloride or Phosphate, or Sodium Phosphate if needed, as per CVVH protocol. Potassium should be added to the substitution fluid to maintain the serum potassium @ 4mmol/L. This can be achieved by adding 15mmol of either KCl or KH₂PO₄ to each 5 litre bag.

The composition is:

- Sodium 140 mmol/L
- Potassium 1 mmol/L
- Chloride 99 mmol/L
- Citrate 14 mmol/L (42 meq/L) Trisodium citrate dihydrate.

**ALL the substitution fluid must be added Pre-Filter, never Post-Filter.**
PERFORMING CVVH

**Step 1 – Flow rates**

1. **Maximum blood flow rate** achievable will vary with catheter size.

Ranges for the different catheters are:

- 6.5F 20-60mls/min. Use for up to 10kg
- 8.5F 50-100mls/min. Use for 11-29kg
- 11F 90-200mls/min. Use for 30kg+

Aim for a blood flow rate of **4ml/kg/min** with a minimum of 20ml/min.

Once blood flow rate established commence substitution flow rate @ **35ml/kg/hr** after 15 minutes and begin filtrate removal @ desired rate.

For different flow rates see Table 1 below.

**Table 1. Initial blood flow rates and substitution fluid flow rates**

<table>
<thead>
<tr>
<th>INITIAL Substitution flow rate</th>
<th>35 ml/kg/hr</th>
<th>48 ml/kg/hr</th>
<th>56ml/kg/hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood flow rate</td>
<td>4 ml/kg/min</td>
<td>5 ml/kg/min</td>
<td>6 ml/kg/hr</td>
</tr>
<tr>
<td>Approximate clearances of urea/creatinine</td>
<td>40 ml/kg/hr</td>
<td>50 ml/kg/hr</td>
<td>60.ml/kg/hr</td>
</tr>
<tr>
<td>INITIAL 10% CaGluconate infusion rate</td>
<td>0.30 ml/kg/hr</td>
<td>0.36 ml/kg/hr</td>
<td>0.42 ml/kg/hr</td>
</tr>
</tbody>
</table>

2. **Filtrate flow rate**

Start at 35ml/kg/hr, i.e. the same rate as the substitution fluid.

Once patient stable, increase filtrate rate to achieve desired fluid balance.

**NB:** Do not have less than 4 ml/kg/min blood flow and 35 ml/kg/hr substitution flow unless the blood flow is limited by access problems and can not be increased to this rate. In this case you need to decrease the substitution fluid rate to match the blood flow rate.

There is evidence from adult studies that show that 35ml/kg/hr filtration rate has a survival advantage over lower rates.

3. **Fluid Removal**

Net fluid balance for the patient is the sum of ALL ingoing fluid minus ALL outgoing fluid.
**Step 2 – Calcium Infusion**

**Plasma ionised calcium must be normalised** prior to starting this treatment (>1.0 mmol/L).

Calcium Gluconate 10% contains 0.22mmol Calcium/ml.
Give a bolus if necessary (0.5 ml/kg 10% Calcium Gluconate over 30 min).

A separate infusion of 10% calcium gluconate (undiluted) is set up into a separate central venous catheter.

*Initial* infusion rate is at 0.36ml/kg/hr of 10% Calcium Gluconate for each 5 ml/kg/min of blood flow.

**Step 3 – Magnesium Replacement**

a) **Plasma magnesium must be normalised prior to starting this treatment (>0.7 mmol/L).** Give a bolus if necessary (0.2 mmol/kg MgSO₄ IV over 60 min).

b) 50% magnesium sulphate (undiluted) 0.2 mmol/kg (0.1 ml/kg) should be given every 12 hours while citrate is running, into a separate central venous catheter (if a spare lumen is available) or into the venous return limb of the circuit. Do not mix it with calcium.

c) The plasma magnesium should be measured 12 hrly. If it falls to 0.7 mmol/L give an extra 0.2 mmol/kg of Magnesium Sulphate and decrease the interval between regular doses to 8 hours while citrate is running.

**Step 4 – Monitoring and Adjusting the Circuit (Post-Filter) Ionised Calcium**

a) Plasma ionised calcium in the circuit must be measured to ensure effective anticoagulation.

b) Take blood samples from the blue port in the return limb of the circuit close to the blue end of the filter (post-filter).

Use a non-heparinised syringe. Analyse it in the blood gas machine to determine the base-line ionised calcium level. **Take a blood sample after 15 min of treatment, then after one hour, and 12-hourly thereafter, to analyse the ionised calcium level.** REPEAT this sampling regimen whenever changes are made to the calcium infusion rate or the substitution fluid rate.

c) The circuit ionised calcium level should be between 0.25 and 0.50 mmol/L. Adjust the substitution flow rate (and thereby the citrate flow rate), Table 2 without adjusting the blood flow rate if the ionised calcium level is outside this range. **NB: This will change the overall fluid balance and you will need to remove more or less fluid per hour if you want the net fluid balance to remain unchanged. Do not go below 35ml/kg/hr of substitution fluid unless limited by blood flow rate.**

Sequential adjustments may be needed before stabilisation of the circuit ionised calcium.
Table 2. Adjusting the citrate infusion rate (i.e. the substitution flow rate)

<table>
<thead>
<tr>
<th>Circuit ionised calcium (Ca)</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.25 mmol/L</td>
<td>Decrease substitution rate by 10%</td>
</tr>
<tr>
<td>0.25-0.50 mmol/L (Optimum)</td>
<td>No adjustment</td>
</tr>
<tr>
<td>&gt;0.5 mmol/L</td>
<td>Increase substitution rate by 10%</td>
</tr>
</tbody>
</table>

Do not adjust blood flow rate

Step 5 – Monitoring and Adjusting the Systemic (Patient) Ionised Calcium

d) Arterial or venous blood gases from a separate arterial or venous line should be performed hourly initially, to measure systemic ionised calcium. Ionised calcium must be kept in the range 0.9-1.2 mmol/L. Adjust the separate calcium gluconate infusion according to Table 3. Sequential adjustments may be needed.

Table 3. Adjusting the Calcium Gluconate Infusion Rate

<table>
<thead>
<tr>
<th>Systemic ionised calcium (Ca)</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1.2</td>
<td>Decrease Ca Gluconate rate by 10%</td>
</tr>
<tr>
<td>1.0-1.2 mmol/L (optimum)</td>
<td>No adjustment</td>
</tr>
<tr>
<td>0.8-0.99</td>
<td>Increase Ca Gluconate rate by 10%. Bolus Ca Gluconate if CVS unstable (see below)</td>
</tr>
<tr>
<td>&lt;0.8</td>
<td>Give 0.3ml/kg over 10 min and increase Ca Gluconate rate by 10%</td>
</tr>
</tbody>
</table>

Record both the circuit ionised calcium and the patient’s ionised calcium in the respective lines on the CVVH sheet.

Sample patient ionised calcium hourly until stable. After 4 hours the hourly sampling rate may be decreased to 2 or 4 hourly if the ionised calcium is stable.

Changing the clearance (filtrate rate)

To increase clearance increases in the substitution flow (and filtrate flow) must be accompanied by a proportionate increase in blood flow, in order to keep the ratio between blood flow and citrate flow constant. (See table 1).

Discuss this with the intensivist.

If you change the prescription for the filtrate and blood flow (because you want a higher clearance, for example), then revert to hourly sampling until stable again.

Other monitoring

Electrolytes

Magnesium (total) should be checked 12-24 hourly.

Sodium should be checked every 6-12 hours.
Calcium (total) should be checked 12-24 hourly, and in addition if more than two sequential increases in calcium chloride infusion rate have been needed, or if metabolic acidosis with rising anion gap occurs. See Acid/base below.

**Acid-Base**

Citrate is completely metabolised in most patients with normal liver function.

A rising anion gap in a patient with a rising total calcium but a falling ionised calcium (despite increasing the calcium chloride infusion) is caused by citrate accumulation ("citrate lock"). This is more likely in patients who have poor liver function and those receiving large amounts of blood products (these can contain large amounts of citrate). Acidaemia is also likely to develop, with a falling bicarbonate, an increasing anion gap, and a decreasing base excess. (Under normal circumstances the citrate in the circuit blood will cause an anion gap which is 5-7 meq/L greater than the patient's anion gap. Therefore in assessing an anion gap it is important to do so on the patient's blood not a circuit blood sample.)

Citrate lock can only be managed by decreasing the citrate, i.e. substitution, fluid flow rate. REMEMBER this should not be less than 35ml/kg/min. If you need to continue at the same rate of filtrate removal then substitute the decreased citrate fluid with either NaCl or NaHCO₃ containing fluids depending upon the serum Na and bicarbonate concentrations.

In some patients this situation continues to worsen and citrate anticoagulation may have to be abandoned and replaced by heparin anticoagulation and bicarbonate replacement fluid.

Some patients with normal liver function may become alkalotic due to overproduction of bicarbonate from the citrate load.

If this occurs use 0.45% or 0.9% saline as some of the replacement solution. Discuss with the intensivist.

**Stopping CVVH with citrate**

Cease the Calcium and Magnesium infusions immediately after ceasing citrate substitution fluid. Recheck plasma total and ionised calcium and total magnesium after 1 hour and 6 hours.

Any of the findings below are an indication to alter treatment. Inform the PICU registrar or Consultant if any of the following.

- Ca⁺⁺ < 0.8 mmol/L or > 1.5mmol/L
- Total serum Ca > 3 mmol/L
- Na⁺ < 130mmol/L or Na⁺ > 150mmol/L
- HCO₃⁻ > 35mmol/L
- pH < 7.3 or pH > 7.5
- Base Excess < - 5
- Patient Anion Gap > 8mmol/L
NOTES

1. CHANGING CLEARANCE

To increase clearance you need to increase the blood flow rate and maintain the ratio of substitution fluid rate to blood flow rate as per table 1. These are the starting values which are then adjusted as per tables 2 and 3.

2. CITRATE LOCK

If citrate lock is developing as evidenced by acidosis, increased anion gap, and increasing ratio of total:ionised calcium then you need to decrease citrate delivery. It is important that the substitution fluid rate is kept at not less than 35ml/kg/hr.

To achieve this and not give excess citrate then some of the substitution fluid will need to be given as either Hemosol (if patient acidotic), 0.9% saline (if patient alkalotic and serum sodium normal), or 0.45% saline (if patient alkalotic and serum sodium high).

This fluid will have to be given and accounted for outside of the Aquarius fluid balance.

A good starting dose is to replace 1/3 of the citrate substitution fluid with one of the above fluids.

3. RECORD KEEPING

All patients need to have a data collection sheet completed for EACH filter that they use while on CVVH.
Trial of Citrate – Evaluation form

Use one of these forms for each circuit/filter

Name: _______________________  Weight: ________________

Attach Patient Sticker Here

Date this circuit started: ________________  Date this circuit ended: ________________

Anticoagulation Used: ________________

Reason for CVVH: __________________________________________________________

Why did this circuit end (routine change, rising TMP or Rb, CVVH stopped, sudden clotting?)
__________________________________________________________________________
__________________________________________________________________________

<table>
<thead>
<tr>
<th>Date</th>
<th>Time</th>
<th>Blood flow rate</th>
<th>Substit.flow rate</th>
<th>CaCl₂ flow rate</th>
<th>Why were the above changed?</th>
<th>Caᵢ in circuit</th>
<th>Caᵢ in patient</th>
<th>Anion gap circuit</th>
<th>Anion gap in pt.</th>
<th>Mg in patient</th>
</tr>
</thead>
</table>

Record above information 12 hourly as close to 0600 and 1800 as practicable.

☐ Other comments:
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