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**CITRATE ANTICOAGULATION USING THE**

**FRESENIUS MULTIFILTRATE PRO**

**NHS LOTHIAN PROTOCOL FOR ICU AT RIE, WGH AND SJH**

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**Index Page number**

**Quick reference flow chart on citrate anticoagulation 3**

**Introduction 4**

**Citrate summary 5**

**Citrate protocol 6**

**How to perform citrate anticoagulation**

* **Step 1 - Management of patient’s systemic ionised calcium pre-CVVHD 7**
* **Step 2 – Dialysate flow rate 7**
* **Step 3 – Prescription 8**
* **Step 4 – Treatment and Monitoring 9**
* **Step 5 – Documentation 10**

**Calcium T : I ratio 10**

**Acute liver failure patients 11**

**Metabolic acidosis 12**

**Citrate accumulation 13**

**Citrate accumulation flow chart 14**

**Alternative anticoagulation 15**

**Setting up and Starting MultiFiltrate Pro 16**

**Frequently asked questions/trouble shooting 17**

**References/Disclaimer/Fresenius Contact info 19**

**Prescribing example (picture) 20**

**Abbreviations**

CVVH **-** continuous venovenous haemofiltration

CVVHD **-** continuous venovenous haemodialysis

CRRT – continuous renal replacement therapy

Ci-Ca = Citrate-Calcium

ABG = Arterial blood gas

Calcium T : I = Total calcium divided by ionised calcium

**QUICK REFERENCE FLOWCHART ON CITRATE ANTICOAGULATION**

**Step 5 (see page 10)**

* **Record information on ICU CVVHD monitoring sheet**
* **Check and record Calcium T : I ratio daily**
* **Be alert to unexplained metabolic acidosis and risk of citrate accumulation – see pages 13-14**
* **Patients at risk are acute liver failure and severe lactic acidosis accumulation**

**Step 4 (see page 9)**

* **Start citrate at 4mmol/L and check post filter ionised calcium at 5 minutes. Adjust as per table 4.**
* **Start calcium chloride at dose recommended in table 1.**
* **Check post filter and systemic ionised calcium every 6 hours unless table 4 and table 5 indicate otherwise**

**Step 3 (see page 8)**

* **Prescribe the dialysate flow rate and fluid removal rate on the**

**24 hour chart**

* **Prescribe the following ‘continuous infusions’ within Kardex**
	+ **Calcium chloride, Sodium citrate and Ci-Ca dialysate K4/K2 bags – page 8 + picture 1 (page 20) for info/dose**

**Step 2 (see page 7)**

* **Determine patient’s dialysate flow rate**
	+ **25ml/kg/hour – see table 2**
	+ **35ml/kg/hour in exceptional circumstances – see table 3**

**Step 1 (see page 7)**

* **Normalise systemic ionised calcium (Ca) before starting CVVHD**
* **Check Ca on ABG 1 hr before starting and correct as per table 1**
* **Liver patients may require different protocol – see page 11**

**Introduction**

This protocol should be used for all general critical care patients requiring CRRT in RIE, WGH and SJH.

There are **3 key** changes being instituted in the delivery of CRRT:

**1. Mode of CRRT**

* The new therapy is continuous venovenous haemodialysis (CVVHD) which will replace continuous venovenous haemofiltration (CVVH).
* As a result, there will be differences in the delivery and prescription of CRRT.
* **Note:** CVVHD is a fundamentally different process to CVVH. Pre/post dilution techniques are therefore not applicable in CVVHD.
* According to the renal drug handbook the elimination of drugs in CVVHD and CVVH is similar, therefore the same reduction/adjustment principles should be utilised.
	+ If concerns consult renal drug handbook or pharmacist.

**2. Mode of anti-coagulation**

* Regional Citrate will be the first line anticoagulant for all patients requiring CRRT.

**3. Brand of CRRT device**

* The new Fresenius MultiFiltrate Pro will replace the existing Baxter Aquarius machines.

**Citrate summary**

* Citrate has two roles:
	1. Regional anticoagulation of the circuit
	2. Acid base balance

**1. Regional anticoagulation of the circuit**

* Regional citrate anticoagulation works by the binding of citrate to ionised (free) calcium, thereby forming citrate-calcium complexes within the dialysis circuit.
* As a result, the low level of ionised calcium within the circuit prevents clotting by deactivating the clotting cascade.
* During CVVHD, 50% of the citrate-calcium complexes are dialysed out as waste and the remaining 50% return to the patient.
* The following two processes help to aid normalisation of systemic ionised calcium levels:
	+ A continuous infusion of calcium chloride into the return line of the circuit.
	+ Metabolism of the citrate-calcium complexes by the patient (this releases some of the previously bound ionised calcium).
* The normalisation of the ionised calcium restores the clotting cascade within the patient.

**2. Acid base balance**

* The citrate-calcium complexes that return to the patient are metabolised by the liver and skeletal muscle to bicarbonate and the free ionised calcium is released.
* In view of this generation of bicarbonate, the dialysate bags have a lower level of bicarbonate than was the case in CVVH.
* However, if the patient is unable to metabolise the citrate-calcium complex, a metabolic acidosis develops due to two factors:
	+ Reduced generation of bicarbonate
	+ Citrate accumulation

**Benefits of regional citrate anticoagulation**

* When systemic anticoagulation is contraindicated
* Lower blood flow required – therefore better tolerated in unstable patients
* Longer circuit life
* Reduced nursing work load

**Citrate Protocol**

* Regional citrate will be the first line anticoagulant for all patients requiring CRRT.
* 3% of patients develop metabolic acidosis consistent with citrate accumulation1.
* The following patient groups are examples of those at increased risk of citrate accumulation and **may not** tolerate citrate. However, it is still considered to be first line.
	+ **Acute severe liver failure**
	+ **Severe lactic acidosis**
* For patients suspected of developing citrate accumulation see pages 13-14 for management.
* **Page 11** of this document is specifically for **acute liver failure patients** who have both:
	+ Lactate > 8
	+ Calcium T:I ratio > 2 – **See page 10 on how to calculate**

**How to perform citrate anticoagulation**

**Step 1 – Management of patient’s systemic ionised calcium pre-CVVHD**

* It is important to check and normalise systemic ionised calcium prior to commencing CVVHD. Approximately 1 hour prior to commencing CVVHD, perform an ABG.

* If systemic ionised calcium < 1.12 give a pre-treatment bolus of calcium chloride:
	+ 10mls of calcium chloride 10% in 50mls Nacl 0.9% over 30 mins.
* Then select the starting prescription of calcium chloride from **Table 1**.

(Note: you do not need to repeat an ABG following the bolus dose of calcium)

**Table 1**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Systemic ionised Calcium****(mmol/L)** (**Arterial Line**) | **<1.01** | **1.01 – 1.11** | **1.12 – 1.20** | **1.21 – 1.45** | **>1.45** |
| Calcium chloridepre-treatment bolus? | **Yes** | **Yes** | No | No | No |
| Starting prescription of calciumchloride (mmol/L of filtrate) | 2.2 | 2.0 | 1.9 | 1.5 | 1.4 |

**Step 2 – Dialysate flow rate**

* **The default dialysate flow rate is 25ml/kg/hour (Table 2).**

**Table 2 – Based on approx. 25ml/kg/hour**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Weight**  | **<60kg** | **60-69kg** | **70-79kg** | **80-89kg** | **>90kg** |
| Dialysate flow rate (ml/hr) | 1400 | 1600 | 1800 | 2000 | 2200 |
| Blood flow rate (ml/min)\* | 70 | 80 | 90 | 100 | 110 |
| Citrate dose (mmol/L) | 4.0 | 4.0 | 4.0 | 4.0 | 4.0 |
| Fluid removal rate (ml/hr) | CLINICIAN DECISION ON INDIVIDUAL PATIENT BASIS |

* Only consider increasingdialysate flow rate to **35ml/kg/hour (Table 3)** in the following:
	+ Severe metabolic acidosis: pH < 7 (see page x for more on metabolic acidosis)
		- **Note if the metabolic acidosis is due to citrate accumulation increasing to 35mls/kg/hour may worsen the acidosis**
	+ Severe hyperkalaemia (K+ > 6.5)
	+ Inadequate response to 25mls/kg/hour
	+ Poisoning (e.g. ethylene glycol)

**Table 3 – Based on approx. 35ml/kg/hour**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Weight** | **<60kg** | **60-69kg** | **70-79kg** | **80-89kg** | **>90kg** |
| Dialysate flow rate (ml/hr) | 1800 | 2200 | 2600 | 2800 | 3000 |
| Blood flow rate (ml/min)\* | 90 | 110 | 130 | 140 | 150 |
| Citrate dose (mmol/L) | 4.0 | 4.0 | 4.0 | 4.0 | 4.0 |
| Fluid removal rate (ml/hr) | CLINICIAN DECISION ON INDIVIDUAL PATIENT BASIS |

\*During citrate anti-coagulation the ratio of dialysate flow rate to blood flow rate **should not be changed**. It should always be 20:1 (dialysate flow rate [ml/hr] : blood flow rate [ml/min]). Note the different units. Any change in this ratio will affect citrate delivery or excretion and therefore affect acid-base balance. However in non citrate (i.e heparin) dialysis the ratios will change as the blood flow rate will need to be increased to prevent clotting within the circuit.

**Step 3 – Prescription**

* Prescribe on the 24-hour chart:
	+ Dialysate flow rate (ml/hr) based on patient weight- **see Table 2 or 3**
	+ Fluid removal rate (ml/hr). (This is a clinical decision on an individual patient basis and is **different** from the blood flow rate in tables 2/3)
* Prescribe the following in the continuous infusion section of the kardex (see picture 1):
	+ Calcium chloride 50mmols in 500mls (100mmols/L)
	+ Sodium citrate 4% 1500mls
	+ Ci-Ca dialysate K4 (Potassium 4 mmol/L) Ci-Ca dialysate K2 (Potassium 2 mmol/L)
		- This should only be used for patients with an elevated potassium level >6.5mmol/L. Once the potassium reaches 5mmol/L change back to Ci-Ca dialysate K4 bags.

**Step 4 – Treatment and Monitoring**

**A) Citrate dose**

* Set initial citrate dose to **4mmol/L** of blood.
* **5 minutes** after commencement of therapy check a post filter ionised calcium (**venous/blue sampling port**) to ensure circuit anticoagulated (adjust as per **Table 4**).
* Then check 6 hourly from venous/blue sample port.
* **More frequent checks than 6 hourly** **should not be done** as this will mean changes made earlier to citrate dose will not have had time to take effect.

**Table 4 – Citrate dose adjustment**

|  |  |  |
| --- | --- | --- |
| **Post filter ionised calcium (mmol/L)****(venous/blue port)** | **Change of citrate dose****(per litre of blood)** | **Check post-filter ionised calcium and review****citrate dose after** |
| **> 0.40** | Increase by 0.2 mmol/Land inform medical staff | 6 hours |
| **0.35 – 0.40** | Increase by 0.1 mmol/L | 6 hours |
| **0.25 – 0.34** | No change | 6 hours |
| **0.20 – 0.24** | Decrease by 0.1 mmol/L | 6 hours |
| **< 0.20 or \*\*\*\* or ↓↓↓↓** | Decrease by 0.2 mmol/L | 6 hours |

**B) Calcium dose**

* See table 1 for initial dose and whether pre-treatment required.
* See table 7 for liver patients with lactate > 8 mmol/L and Calcium T:I ratio > 2.
* Systemic ionised calcium level should be taken from the patient’s **Arterial Line**.
* An immediate systemic ionised calcium is not required (unlike post filter calcium).
* First check at 6 hours and then as directed by **Table 5**.
* In patients where there has been a significant fall in systemic ionised calcium more frequent checks may be required.

**Table 5 – Calcium chloride dose adjustment**

|  |  |  |
| --- | --- | --- |
| **Systemic ionised calcium (mmol/L)****(arterial line)** | **Change of calcium dose****(per litre of filtrate)** | **Check systemic ionised calcium and review dose after** |
| **> 1.35** | Decrease by 0.4 mmol/L and inform medical staff | 6 hours |
| **1.21 – 1.35** | Decrease by 0.2 mmol/L | 6 hours |
| **1.12 – 1.20** | No change | 6 hours |
| **1.00 – 1.11** | Increase by 0.2 mmol/L | 6 hours |
| **< 1.00** | Increase by 0.4 mmol/Linform medical staff | **2 hours** |

**Step 5 - Documentation and Monitoring**

* **Use ICU CVVHD monitoring sheet for documentation and results.**
* Record post filter and systemic ionised calcium results as directed by tables 4/5.
	+ **Note in cases of low systemic ionised calcium more frequent checks are required** (see table 5)
* Calculate and record calcium T : I ratio daily

**Calcium T : I Ratio**

* Calculate the ratio of total calcium to systemic ionised calcium **DAILY**
	+ Obtain total calcium from laboratory bloods.

(Note: ***Do not*** correct for albumin)

* + Obtain systemic ionised calcium from most recent ABG.
	+ Calcium T:I Ratio = total calcium divided by systemic ionised calcium.
* Calcium T:I ratio > 2.5 indicates citrate accumulation see page 13.

**Circuit life**

* The circuit should run for a maximum of 72 hours after which a change in circuit is required.

**Acute liver failure patients**

* Check lactate and calculate Calcium T:I ratio (see page 10 for calculation) in all liver patients prior to commencing CVVHD.
* If lactate > 8 and Calcium T:I ratio > 2 use amended table below for initial management of systemic calcium (**Table 7**) and once initiated return to **Table 5** for further management.

**Table 7 – For Use in Liver Patient with Lactate > 8 *and* Calcium T:I Ratio > 2**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Systemic ionised calcium** **(mmol/L)**  | **< 1.01** | **1.01 - 1.11** | **1.12 -1.20** | **1.21 - 1.45** | **> 1.45** |
| **Pre-treatment with** **calcium chloride** | **Yes** | **Yes** | **Yes** | **Yes** | **Yes** |
| **Starting dose calcium chloride (mmol/L)** | **2.4** | **2.2** | **2.0** | **1.5** | **1.4** |

* Review these patients on a regular basis with senior medical staff and observe for signs of citrate accumulation (see pages 13-14 for management):
	+ **Calcium T:I ratio > 2.5**
	+ **Marked drop in systemic ionised calcium**
	+ **Elevated total calcium > 3mmol/L**
	+ **Unexplained metabolic acidosis**

**Coagulopathic liver failure patients**

* In patients with severe coagulopathy as detected on ROTEM or formal laboratory screen it may be appropriate to use CVVHD with no anticoagulation including no citrate.
* Refer to page 15 on how to perform CVVHD with no anticoagulation.

**Metabolic acidosis**

* If the patient is unable to metabolise citrate a metabolic acidosis develops due to:
	+ Reduced generation of bicarbonate
	+ Citrate accumulation
* Any patient is at risk but specifically patients with:
	+ **Acute liver failure**
	+ **Severe lactic acidosis**

**If a metabolic acidosis fails to improve or develops de-novo it is important to distinguish if it is due to a primary metabolic process or due to the accumulation of citrate.**

**Potential causes of metabolic acidosis and actions include:**

* Patients underlying condition:
	+ Treat as appropriate
* CVVHD has not been running long enough:
	+ Recheck acid base in due course
* Inadequate dialysis dose:
	+ Trial of increasing dialysis flow rate to 35mls/kg/hr
	+ **Note if the metabolic acidosis is due to citrate accumulation this increase may worsen the acidosis**
* Citrate accumulation due to impaired metabolism
	+ See pages 13-14

**Citrate accumulation**

**Signs that citrate accumulation is developing include:**

1. **Calcium T:I ratio > 2.5**
2. **Marked drop in systemic ionised calcium (increasing need for calcium replacement)**
3. **Elevated total calcium > 3mmol/L (do not correct for albumin)**
4. **Unexplained metabolic acidosis**
* The Fresenius machine will prompt consideration of citrate accumulation if the infusion dose of calcium chloride is > 2.1mmol/L.
* **See citrate accumulation flow chart on page 14.**

**Why does a Calcium T:I ratio > 2.5 indicate citrate accumulation?**

* A drop in the systemic ionised calcium will occur if the citrate-calcium complexes are not being metabolised and therefore bound calcium is not released as ionised calcium.
* Additional calcium chloride replacement will therefore be required as directed by table 5
* However total calcium increases as all forms of calcium including the calcium that is still bound to citrate are measured by the laboratory analyser.
* This results in a change in the ratio of total body calcium to ionised calcium.
* In summary rising total calcium and falling ionised calcium indicates citrate accumulation and results in a raised T : I ratio

**Management of Citrate Accumulation Flow Chart - (Figure 1)**

**Check for citrate accumulation daily or more often if you suspect it may be occurring**

**Features of citrate accumulation (any of):**

1. **Calcium T:I ratio > 2.5**
2. **Marked drop in systemic ionised calcium**
3. **Elevated total calcium > 3mmol/L**
4. **Unexplained metabolic acidosis**

**YES**

**REDUCE CITRATE DOSE**

* Allow post filter ionised calcium to rise to 0.35 - 0.45
* To do this reduce citrate dose by 0.2mmol/L
* Recheck post filter ionised calcium after 30 minutes
* If not within above range reduce citrate dose by further 0.1 -0.2mmol/L and recheck in 30 minutes
* Once within reference range continue treatment
* After 4 hours check for continuing features of citrate accumulation (the 4 features above)
* If there has been a reasonable improvement in these features it is probably appropriate to continue citrate for a further 4 hours and reassess

**NO IMPROVEMENT**

Patient improved as above

Continue Ci-Ca dialysis

Deselect Ci-Ca treatment and revert to heparin. This is a medical decision

See page 15 for how to do this.

Continue Ci-Ca citrate dialysis but remain vigilant with 6 hourly checks

**Alternative anticoagulation**

**1. CVVHD with heparin**

**A change to heparin can be made in the following circumstances:**

* If citrate accumulation does not respond to corrective measures
* Consultant request
* Patient requires systemic IV heparin for another indication
	+ **Although the majority of centres will still run citrate in these cases as it is only regional anticoagulation. This is a senior medical decision.**

**To start heparin:**

* Heparin can be given via the Fresenius machine or via a separate infusion pump
	1. Note sometimes the Fresenius machine does not recognise different 50mls syringes – hence a separate infusion pump may be required
* Deselect citrate (Ci-Ca) from the treatment screen (if already on citrate) when ready to start heparin
* **You must:**
	1. **Change the dialysate bags to Accusol 4 or Multibic 4 (but NOT Accusol 0)**
		+ **You must not** use the Ci-Ca dialysate bags as this will cause a **life threatening hypocalcaemia**
	2. **Increase the blood flow rate to a minimum of 250mls/min**
		+ The dialysate flow rate to blood flow rate **no longer** needs to be maintained at 20:1 like in citrate dialysis as per tables 2/3. The 20:1 ratio was required in citrate for acid base control, however as citrate has been deselected this ratio is no longer required.
		+ The blood flow increase is required to prevent the circuit clotting. Previously pre-dilution was used to help with this but as the switch has been made to CVVHD this is not possible.
		+ Due to the lack of pre-dilution you may find that higher doses of heparin are required compared to the previous CVVH modality.
		+ If extra clearance is required you can increase the dialysate flow rate to a maximum of 4.8L (medical decision)

**2. CVVHD with no anticoagulation**

* This maybe appropriate in patients with severe coagulopathy
* **As above again ensure:**
	+ **Dialysate bags are Accusol 4 or Multibic 4 (but NOT Accusol 0)**
		- **You must not** use the Ci-Ca dialysate bags as this will cause a **life threatening hypocalcaemia**
	+ **Increase the blood flow rate to a minimum of 250mls/min** (you do not need to change the dialysate flow rate)

**Setting up and Starting MultiFiltrate Pro**

**Ensure you have the following:**

1. 1 Litre 0.9% Nacl
2. 1500ml Sodium Citrate 4%
3. 5L Ci-Ca Dialysate bags K4 (only K2 if potassium > 6.5mmol/L) x 2
4. Calcium chloride 50mmols in 500mls
5. Circuit
6. Red and Blue Y connectors
7. AV 1000 filter

**To start:**

1. Switch on machine
2. Wait for function test to be completed
3. Select new treatment
4. Select CVVHD with Ci-Ca anticoagulation
5. Confirm all conditions have been met
6. Follow step by step guide to line the machine
7. Measure post filter ionised calcium 5 minutes after starting to confirm there is adequate anticoagulation and adjust accordingly as per table 3

**Notes**

1. The citrate and calcium lines need to be clamped initially to allow a vacuum to be created. The clamps should be moved to the bag connection end of the line and clamped.
2. The citrate and calcium lines are primed first.

**Frequently asked questions/Trouble shooting**

Note the trouble shooting guide is integrated into the Fresenius MultiFiltrate Pro and therefore there is not a paper version.

**Filter clogging and becoming less efficient**

* As filter pores clog more citrate is delivered to the patient as less is dialysed out
* This results in an increased generation of bicarbonate
* Signs of an old/clogging filter include
	+ Rising bicarbonate
	+ Reduced clearance of urea and creatinine
	+ Rising TMP and pre-filter pressure

**What happens if you use the wrong dialysis solution during citrate (Ci-Ca) therapy?**

* If you use Accusol or Multibic during Ci-Ca therapy you may encounter
	+ Systemic bicarbonate increasing
	+ Systemic ionised calcium increasing
	+ Post filter ionised calcium high with citrate requirements increasing

**What changes need to be made if a patient is disconnected from the circuit**

* Providing there has been no change in the patient’s clinical state and it is not more than 4 hours since the circuit was disconnected, patients can be reconnected using the previous dialysate and bloods flows, and citrate and calcium doses.

**What methods of temporary disconnection are available?**

**Method 1 –** Wash back and recirculate

The maximum disconnection time with this method is **4 hours**

**Requirements**: 1 litre bag of sodium chloride 0.9%, three way tap or Y connector and single spike adapter, dressing pack and equipment to flush catheter.

1. Press **STOP**
2. Disconnect the arterial line (RED)and connect to the Y connector or three way tap attached to the sodium chloride 0.9% bag
3. Press **START/RESET** this will restart the blood pump and wash back blood to the patient.
4. The optical detector will detect sodium chloride 0.9% solution. The blood pump will stop. A yellow warning will be displayed informing you that the above change has been detected.
5. Press **START/RESET** the machine will then ask you to confirm if you have interrupted the treatment. Press **YES**. The blood pump will now restart.
6. Decide how much blood you want to be returned to the patient. Press **STOP** when you have reached the amount you wish to be returned.
7. Disconnect the venous line **(blue)** from the patient and connect to the Y connector or three way tap attached to the sodium chloride 0.9% bag.
8. Press **START/RESET** and the machine will then be recirculating. (Balancing will automatically switch off).
9. Turn ultrafiltration/fluid off to 0. **Remember to turn it back on when you reconnect the patient.**

**To reconnect the patient**

1. Press **STOP**
2. Disconnect the arterial (RED) and venous (BLUE) lines from the sodium chloride 0.9% bag and connect to the patient access as per protocol.
3. Press **START/RESET** and the blood pump will restart.
4. A yellow warning will be displayed when the optical detector has detected blood.
5. Press **START/RESET** this will restart the blood pump (Balancing will automatically switch on)
6. Turn ultrafiltration/fluid off to the desired removal rate.

**Method 2 –** Re-circulate with whole blood – e.g when transferring bed space

This method can be used for disconnections last **not more than 30 minutes**

**Requirements:** Blue adapter from kit (or three way tap or Y connector).

1. Press **STOP,** this will stop the blood pump
2. Disconnect the arterial (RED) line and connect it to the adaptor
3. Disconnect the venous (BLUE) line and connect it to the other side of the blue adapter
4. Press **START/RESET** this will restart the blood pump
5. Turn ultrafiltration (UF) (fluid off) to 0. **Remember to turn it back on when you reconnect the patient.**

**Disclaimer**

This protocol has been developed using input from the Fresenius protocol and from discussion with learned centres throughout the UK. As our experience with this protocol increases, changes will be made to ensure this protocol fits our patient population.

**References**

1. Khadzhynov D et al. Incidence and outcome of metabolic disarrangements consistent with citrate accumulation in critically ill patients undergoing continuous venovenous hemodialysis with regional citrate anticoagulation. *J Crit Care* 2014;29:265-71
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3. Bai, M., Zhou, M., He, L. et al. Citrate versus heparin anticoagulation for continuous renal replacement therapy: an updated meta-analysis of RCTsIntensive Care Med (2015) 41: 2098.

**Contacts**

* Fresenius MultiFiltrate Helpline: (Mon- Fri 09:00 – 17:00) **01623 445104**
* Fresenius MultiFiltrate Helpline: (Out of hours) **0870 458 7971**

**PICTURE 1**

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