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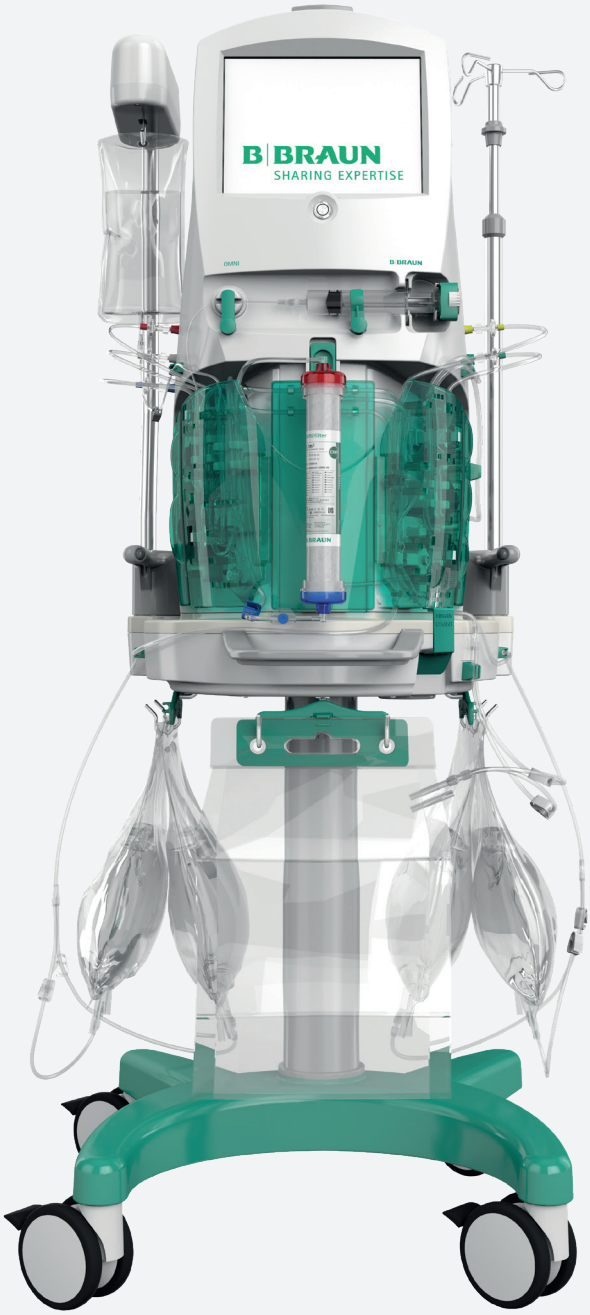


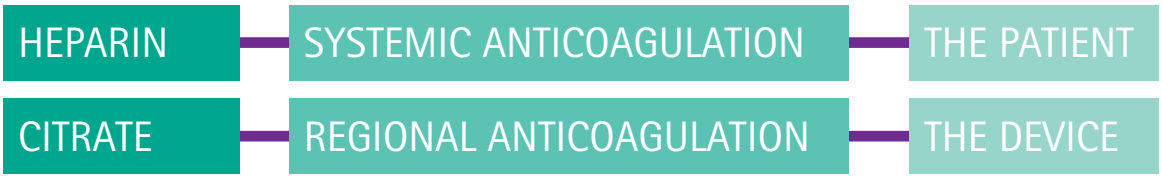
B. BRAUN OMNI®

ACUTE BLOOD PURIFICATION

CITRATE ANTICOAGULATION
PRE-COURSE READING MATERIAL[1]

Regional Citrate Anticoagulation (RCA)

Historically, Continuous Renal Replacement Therapy (CRRT) has utilised heparin as its first line anticoagulant, however, internationally, there has been a movement towards citrate away from heparin.



There will always be a place for heparin in the practice of CRRT, however, heparin anticoagulates both the machine and the patient (to some extent) which can be seen as a major drawback in most cases. On the other hand, citrate is known as a regional anticoagulant, meaning that only the device is anticoagulated.

Heparin pros and cons[2]

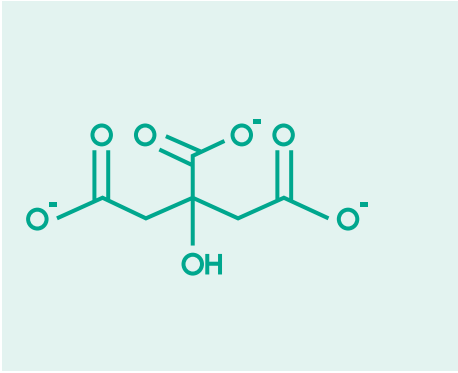
PRO	CON
Low cost of drug	Premature circuit clotting
Familiar	Reduced circuit life
Simple protocols	Reduction in renal dose delivery
Routinely monitored	Increased nursing workload
Easily reversed (protamine)	Increased overall therapy costs
	Thrombocytopenia
	Heparin induced thrombocytopenia
	Increased need for transfusions

Citrate pros and cons[2,11]

PRO	CON
Decreased circuit clotting	High cost of calcium
Increased circuit life	Unfamiliar
Better renal dose delivery	More complicated protocols
Reduced nursing workload	No routine patient monitoring
Overall therapy more cost effective	No reversal agent
Less bleeding risk – fewer transfusions	Metabolic alkalosis (in normal metabolism)
	High anion gap metabolic acidosis (in liver dysfunction)
	Hypocalcaemia (Ca_2^+)
	Hypernatraemia (Na^+)
	Hypomagnesaemia (Mg^+)

Citrate

Citrate is a small molecule of a similar size to urea – 189Da. This means that it is readily excreted via the semi-permeable membrane and lost in the effluent. Its half-life is 36 minutes +/- 18 minutes. There is a small concentration in the blood and it is also what's used in cold stored blood products.



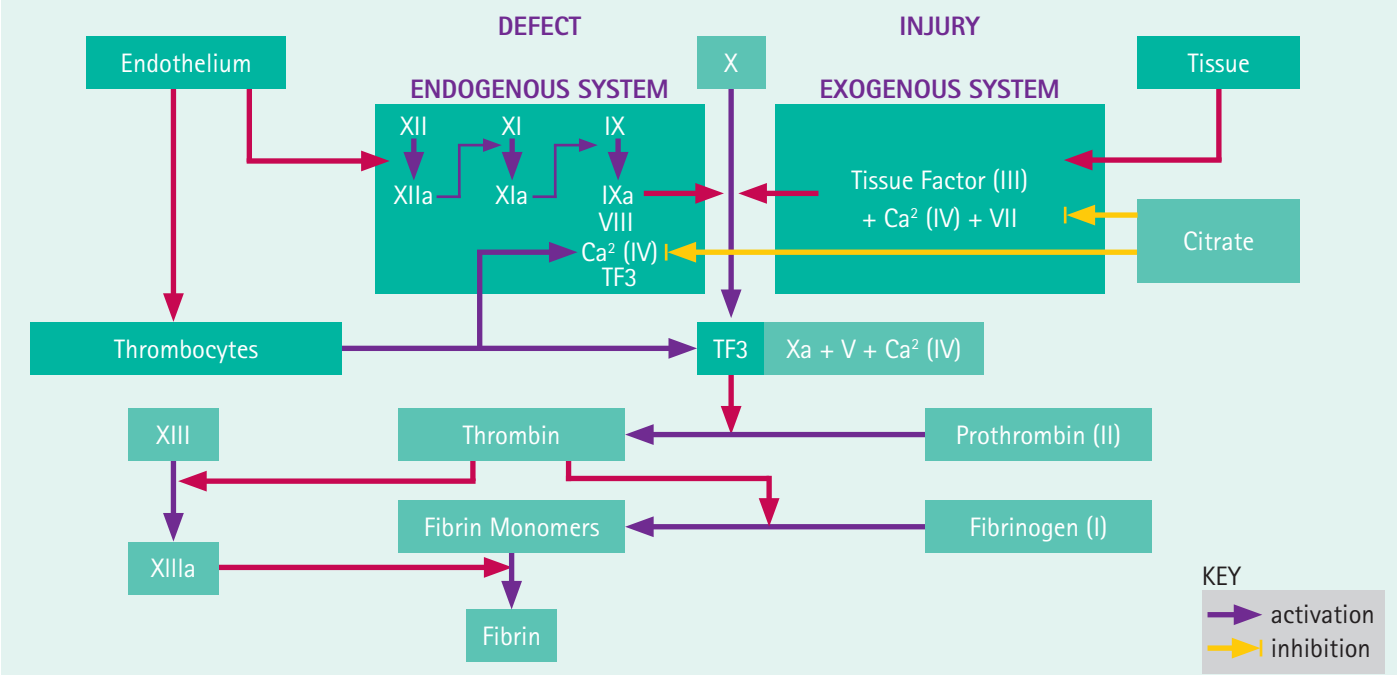
According to KDIGO[3] (Kidney Disease Improving Global Outcomes), citrate should be used as the first line anticoagulant if staff have received suitable training and a robust protocol is in situ. A lot of research is now available demonstrating the efficacy of citrate (feel free to do your own reading). Overall, the research points in the same direction. Citrate is associated with fewer complications than heparin, is associated with a longer filter life which will help deliver a more accurate renal dose and over time, will work out to be a more cost effective therapy[4,12].

On the OMNI, citrate is not compatible with all therapy types. If you are using CVVH, then you will have to use an alternative anticoagulant such as heparin. This is on account of the high blood flows which are used in CVVH.

	HEPARIN	NO ANTICOAGULANT	CITRATE
CVVH	✓	✓	✗
CVVHD	✓	✓	✓
CVVHDF	✓	✓	✓

How does citrate work?

What's most important to understand, is that ionized calcium is integral to the clotting cascade (in both the endogenous and exogenous system). Citrate is known as a natural calcium chelator, it therefore binds or 'chelates' to ionized calcium, rendering it 'inactive' and impairing anything below that stage of the clotting cascade from taking place.



The idea is not to bind absolutely every molecule of ionized calcium as this would cause the patients ionized calcium levels to fall dangerously low, and in turn, this could cause vasoplegia, decreased myocardial contractility and eventually cardiac arrest. The intention is to reduce the concentration of ionized calcium in the haemofilter to a level low enough to extend the clotting time. In a normal, healthy patient with an ionized calcium of 1.0 - 1.2 mmol/l, the clotting time is approximately 200s. The evidence and research has demonstrated that if we are able to bring the ionized calcium concentration inside the device, to as low as 0.25 - 0.4 mmol/l, clotting time will be increased to around 1200s. Hypothetically, this will allow enough time for the blood to enter the circuit, be cleaned (via ultrafiltration, adsorption, diffusion or convection) and be returned to the patient via the venous line without any clot formation[5].

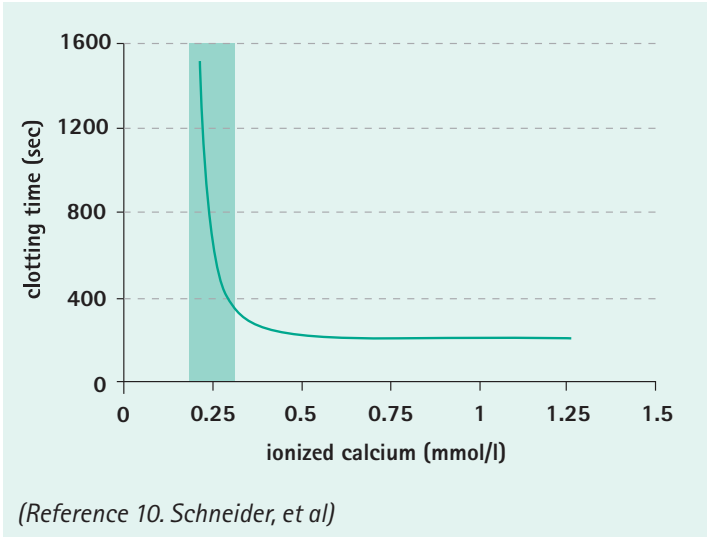
Citrate

How does citrate work?[2,6]

In the graph (right), you can see that clotting time is approximately 200 seconds when ionized calcium concentration is between 1.0 - 1.25 mmol/l. When an ionized calcium concentration of 0.25 mmol/l is achieved, clotting time is extended to 1200 seconds.

Studies have demonstrated that the ideal amount of citrate to add to the blood in order to achieve an ionized calcium concentration of 0.25 - 0.4 mmol/l is **4 mmol citrate/l blood,** this is known as the **dose,** *remember to take a note of the units*[6].

Citrate **dose** is input into the OMNI machine by the bedside user, however, the volume of citrate that is delivered will be calculated based on the volume of blood being filtered. This is determined by the **blood flow.** For this reason, we do not titrate blood flow when using citrate anticoagulation outside of the prescription, strict adherence of the protocol must be observed.



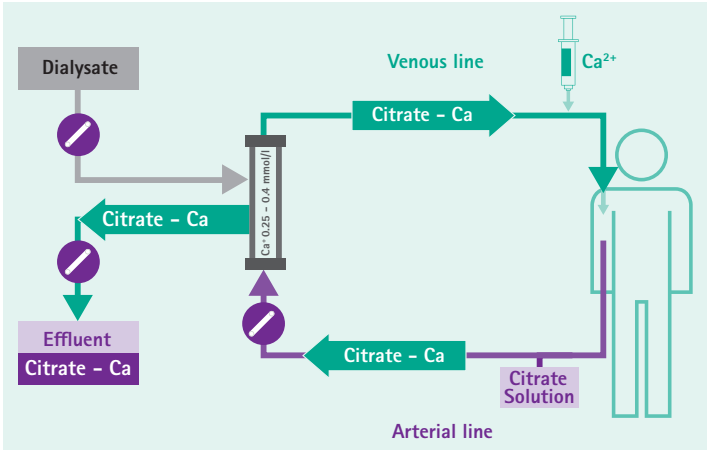
(Reference 10. Schneider, et al)

It is possible to make adjustments to the **citrate dose** based on the **post filter ionized calcium level.** Some hospitals choose not to monitor this and therefore do not titrate citrate dose. This will be determined by your specific trust protocol. Be cautious of recent alarms when taking blood gases as some alarms may cause stops to your anticoagulant and therefore blood gas results may not be accurate.

Maintaining a safe calcium level

When using citrate anticoagulation, it is necessary to simultaneously infuse a calcium replacement. Most often this is in the form of calcium chloride. The concentration is determined by the trust but it is usually 500 mmol/l. This concentration is configured into the OMNI and cannot be altered by the user, so always dilute to the agreed concentration.

As discussed above, much of the patient's ionized calcium is chelated to citrate inside the filter circuit during regional citrate anticoagulation (RCA). Once the citrate and calcium are bound, the molecule is then known as a citrate calcium complex. Citrate calcium complexes are weak, non-volatile acids. A reasonable percentage of these citrate calcium complexes are lost in the effluent during CRRT on account of their size and sieving-coefficient. Based on research, we can estimate that approximately 1/3 of the citrate calcium complexes will be lost this way[11].



(Reference 10. Schneider, et al)

Clearly this is too much calcium for the patient to lose and maintain haemodynamic stability, therefore, we optimise the patient's ionized calcium based on the volume of effluent produced. Effluent is made up of dialysate fluid, pre-filter substitution fluid (depending on which therapy you are using) and ultrafiltrate, also known as net fluid removal (NFR). When you adjust the volume of any of these aforementioned flows, the volume of calcium delivered will be proportionally adjusted. The bedside user is responsible for inputting the dose of calcium chloride, usually this dose is **1.7 mmol/l effluent** at the beginning of the therapy (check your specific protocol). *Remember to take note of the units.* The rate at which calcium is delivered will be adjusted automatically by the OMNI when adjustments are made to the effluent volume.

It is possible to make adjustments to the **calcium dose** based on the **patients systemic ionized calcium level** and the dose adjustment will be determined by your specific trust protocol. Be cautious of recent alarms when taking blood gases from your patient. Some alarms may cause stops to your anticoagulant and therefore blood gas results may not be accurate.

Indications and contraindications

According to KDIGO[3], citrate should be used as the first line anticoagulant in all patients receiving CRRT unless they have a contraindication. All trusts will compile their own unique list of contraindications and cautions.

Contraindications:

- Acute liver failure
- Severe lactic acidosis
- Severe metabolic alkalosis

There is emerging research highlighting that citrate can be safely used, even in patients with acute liver failure, but always follow your protocol and liaise with the multi disciplinary team (MDT) when choosing the appropriate anticoagulant[7,13].

Cautions:

- Chronic liver disease
- Post hepatic resection
- Chronic hypocalcaemia
- Moderate lactic acidosis
- Deranged serum sodium

Reduce the threshold at which you change from citrate to an alternative anticoagulation if there is a question over ineffective metabolism.

Rationalising citrate contraindications

In order to understand why the above circumstances make a patient contraindicated for citrate, we must first understand how citrate is metabolised.

We know that approximately 1/3 of the citrate calcium complexes are removed in the effluent, but that means that the remaining 2/3 are returned to the patient, and these need to be broken down.

Indications and contraindications

Citrate metabolism

The bulk of the citrate metabolism takes place in the liver. There is also a share of the metabolism occurring in the skeletal muscle and in the kidneys but during Acute Kidney Injury (AKI), this will be ineffective.

Citrate comes in a 2 litre bag of Citrasol 4% Trisodium, stabilised in an carbonic acid buffer. When the citrate calcium complex is broken down, the ionized calcium will be re-released back into the patients blood. The equation for metabolism is below:

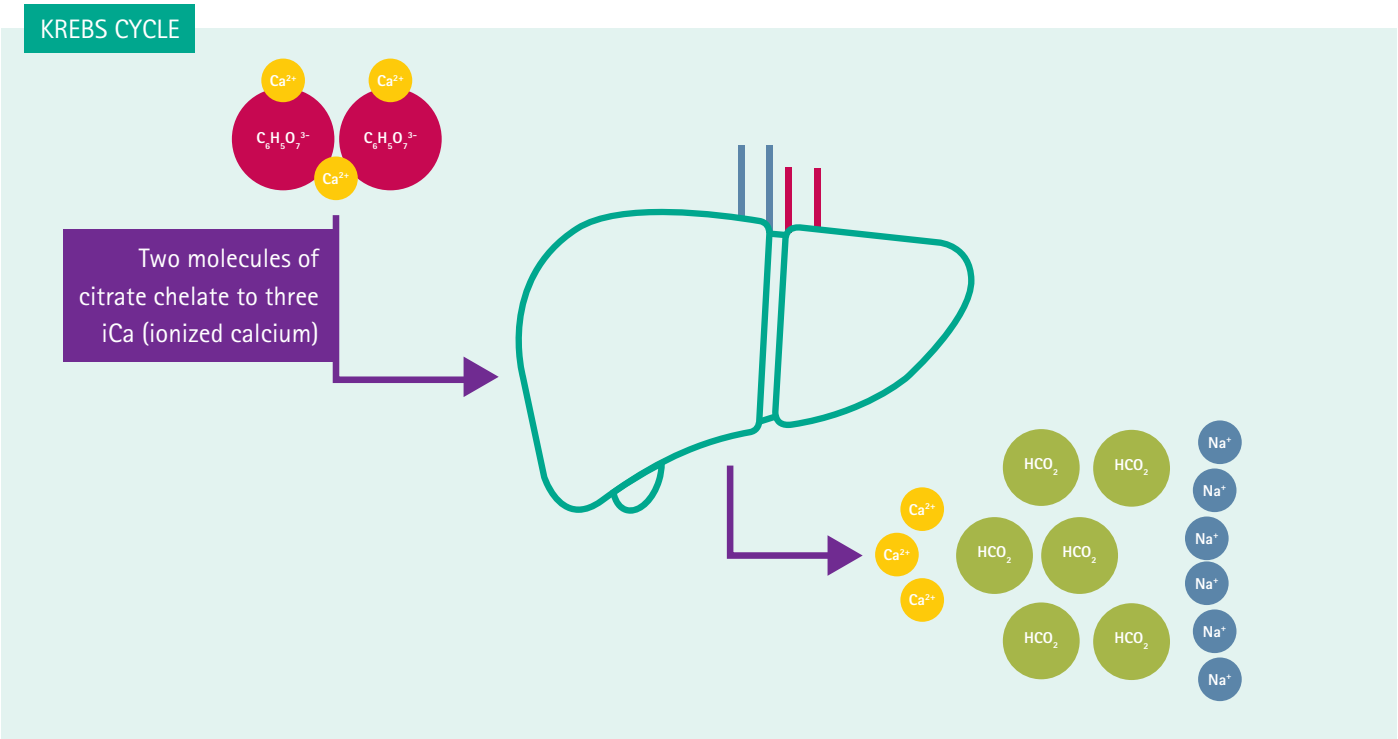
$$3Na^{+} + C_6H_5O_7^{-3}\ (\text{citrate}) + H_2CO_3\ (\text{carbonic acid}) \Leftrightarrow C_6H_8O_7\ (\text{citric acid}) + 3Na^{+} + 3HCO_3^{-}$$

You can see that the end products are:

- Citric acid – acid
- 3 Sodium (Na^{+}) - base
- 3 Bicarbonate (HCO_3^{-}) - base

Citric acid is further broken down in the citric acid cycle, which is also known as the Krebs Cycle. The end products of citric acid metabolism are neutral.

Overall, if citrate metabolism is effective, there will be a gross production of base end products causing the patient to become alkalotic. There are times when this can be advantageous in order to counteract AKI induced acidosis[8].



Don't forget

Citrate and citrate calcium complexes are weak non-volatile acids, meaning that the specific effect on the plasma is acidification. If the citrate calcium complexes are metabolized effectively, there will be an increased production of base products. This will result in an alkalotic effect on the patients plasma pH, which can be desirable to a point.

Indications and contraindications

CONTRAINDICATION	RATIONALE
Acute liver failure (ALF)*	Citrate calcium complexes (CCC) are broken down in the liver, in severe liver dysfunction, you may see accumulation of CCC causing acidosis and calcaemia.
Lactic acidosis	High lactate is indicative of an inefficient Kreb Cycle which is vital in citric acid metabolism.
Severe metabolic alkalosis	Three molecules of HCO_3^- are produced for each molecule of citrate. Increases in HCO_3^- over 40 and pH above approximately 7.5 (depending on the trust) can result in undesirable compensatory mechanisms in the body.
Hypocalcaemia	Citrate chelates ionized calcium and therefore induces a degree of hypocalcaemia, which can be extremely challenging to safely manage in patients with chronically deranged calcium levels.
Deranged sodium	Three molecules of Na^+ are produced for each molecule of citrate and therefore, RCA can cause serum sodium levels to climb quickly. In patients with low sodium, this rapid shift can cause cerebral oedema. In patients with high sodium, this will cause further elevation and can be associated with dropped GCS, prolonged use of mechanical ventilation, long ICU stays and poorer outcomes.

Don't forget

Acute liver failure is a specific diagnosis and does not refer to all patients presenting with deranged liver function. *Acute liver failure refers to the development of severe acute liver injury with encephalopathy and impaired synthetic function (coagulopathy- INR of ≥ 1.5) in a patient without cirrhosis or pre-existing liver disease*[9,14].

Calcium definitions

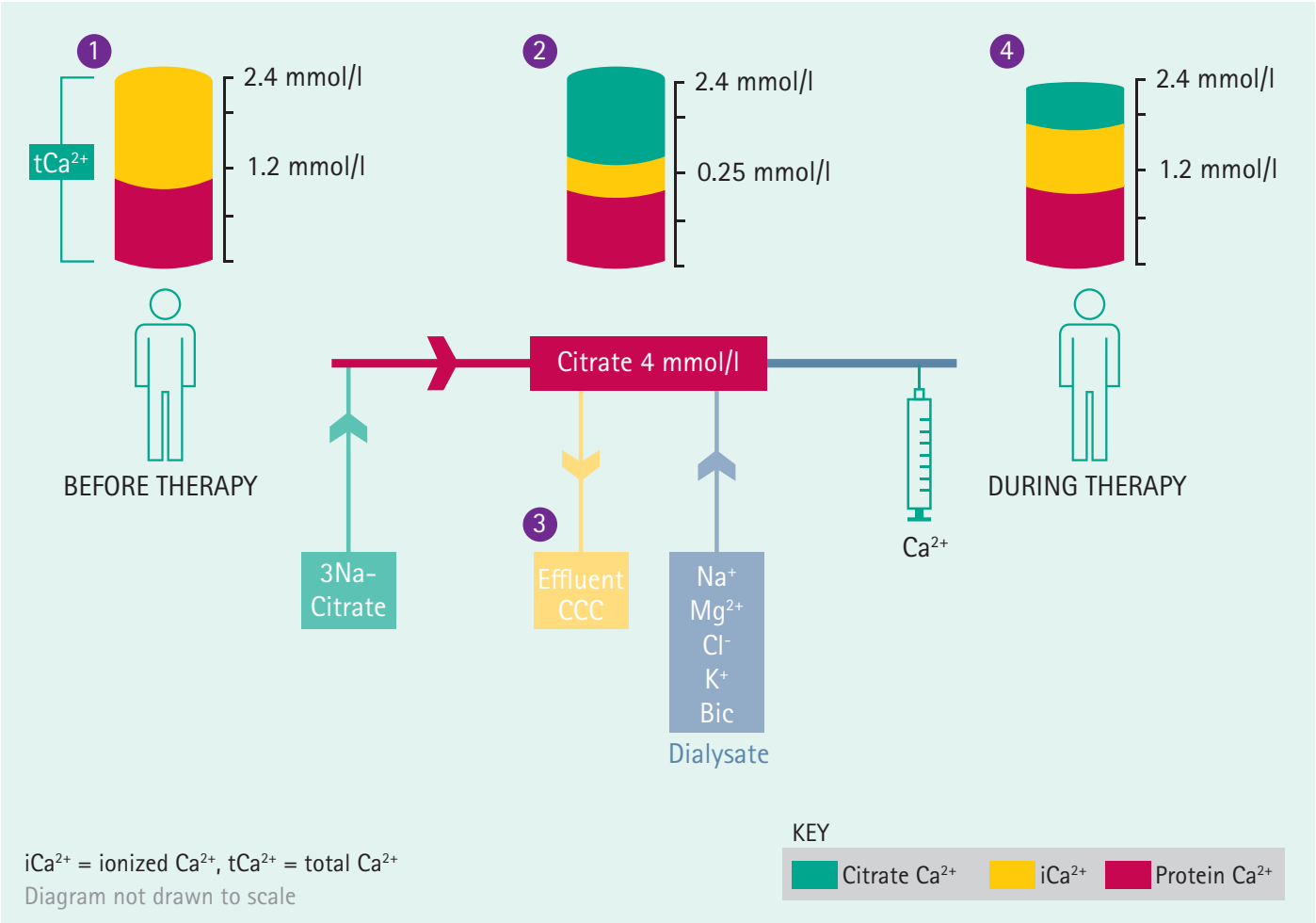
Free calcium	is not bound to proteins = iCa
Bound calcium	is calcium bound to a protein
Total calcium	is both free & bound calcium = tCa
Adjusted calcium	is total calcium after consideration of serum albumin level = AdjCa
Calcium ratio	tCa/ iCa

Calcium ratio is essentially an early warning system to notify you if there is a problem with your patients ability to metabolise citrate. Check your protocol for trust specific guidance. Most trusts will ask you to perform a calcium ratio at least once per day. You can perform another calcium ratio if you start to have concerns about your patients ability to metabolise citrate.

For the purposes of the calcium ratio, always use tCa rather than AdjCa. The tCa and iCa used to calculate your calcium ratio should have been taken within at least one hour of each other to ensure accuracy. A calcium ratio of >2.5 will trigger action in most trusts. Some trusts may use a slightly different calcium ratio.

Calcium concentration

Changes to calcium concentration throughout therapy



The above diagram is an example of citrate anticoagulation in CVVHD

1. Prior to treatment, the patients iCa is 1.2 (the yellow wedge), their tCa is 2.4, so we can conclude their protein bound Ca is also 1.2 (the red wedge). The protein bound Ca is not interacting with citrate so the concentration shouldn't change much throughout RCA.

2. When 4 mmol citrate/l blood is added, iCa begins to chelate to citrate and form citrate calcium complexes. The iCa in the haemofilter reaches a concentration of 0.25. The remainder of the iCa is still present in the blood but it is now chelated to citrate (the green wedge). Protein bound calcium is unaffected.

3. Approximately 1/3 of the citrate calcium complexes are lost in the effluent and this is what is compensated for by the calcium substitution. The green wedge will be reduced by 1/3.

4. The blood that goes back to the patient contains 2/3 of the citrate calcium complexes, the iCa has been partially reoptimised based on the volume of effluent.

5. The expectation is that the citrate calcium complexes will be metabolised and all of the iCa chelated to the citrate will be released and you will get a return to the status quo i.e. 1

Troubleshooting metabolic derangements

There are two well understood complications of RCA.

1. Net citrate overload[10]

Net citrate overload is caused when either too much citrate is delivered to the patient or too little citrate is cleared from the patient. In net citrate overload, the patient has an effective metabolism of citrate and therefore they produce a large volume of base end products. This is indicated by an isolated metabolic alkalosis. Knowing that the volume of citrate delivered is determined by blood flow, it is logical to conclude that reducing the blood flow will reduce the volume of citrate delivered.

In addition, knowing that 1/3 of the citrate calcium complexes are removed via the effluent, it is logical to conclude that by increasing effluent production (i.e. increasing dialysate flow), will increase citrate clearance.

Consult your protocol, it will prescribe the specific values to decrease or increase by depending on the patient's clinical status. *Don't forget to inform the MDT and document the rationale for all of your actions.*

- Benign and easily resolved
- Decrease blood flow and therefore decrease citrate volume
- Increase dialysate flow and therefore increase citrate clearance
- Anticipate that it can take four - six hours to see a change to the patients metabolic status after altering either blood flow or dialysate flow
- Systemic ionized calcium should not be a concern because iCa bound to citrate will be released during metabolism
- Calcium ratio will remain in normal range

2. Citrate accumulation[10]

Citrate accumulation is of more concern and can be fatal if not managed quickly and effectively. In citrate accumulation, the patient has a hindered ability to metabolise the citrate calcium complexes and therefore they begin to accrue in the patients blood. On account of them not being broken down, the iCa remains chelated to the citrate and therefore the patients systemic iCa begins to fall.

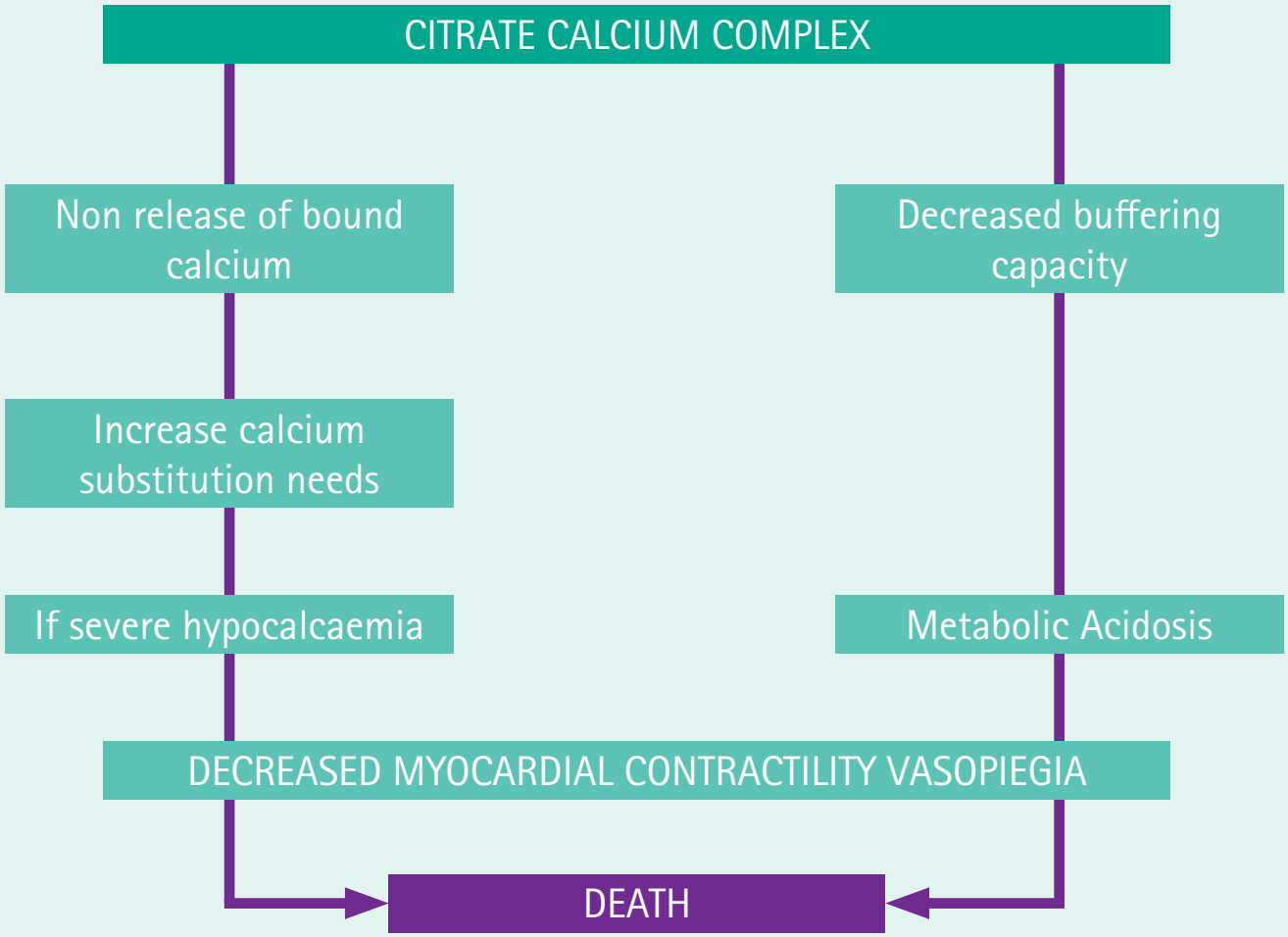
This will prompt you to increase your calcium substitution. Calcium ratio is the most dependable indication of citrate accumulation, sometimes known as citrate toxicity. You may also see other concerning trends which can prompt you to check your calcium ratio.

- New or unexplained acidosis
- Increasing lactate
- Static or downward trend in Na^{+}
- Static or downward trend in HCO^{3-}
- Falling systemic iCa
- Increasing calcium substitution needs
- Increase in calcium ratio >2.5

Recommended actions

If you suspect citrate accumulation, you can send a repeat tCa and recalculate your calcium ratio at any time. If your pH falls below a specified value then you will be prompted to take action to reverse the accumulation. The management is similar to that of net citrate overload:

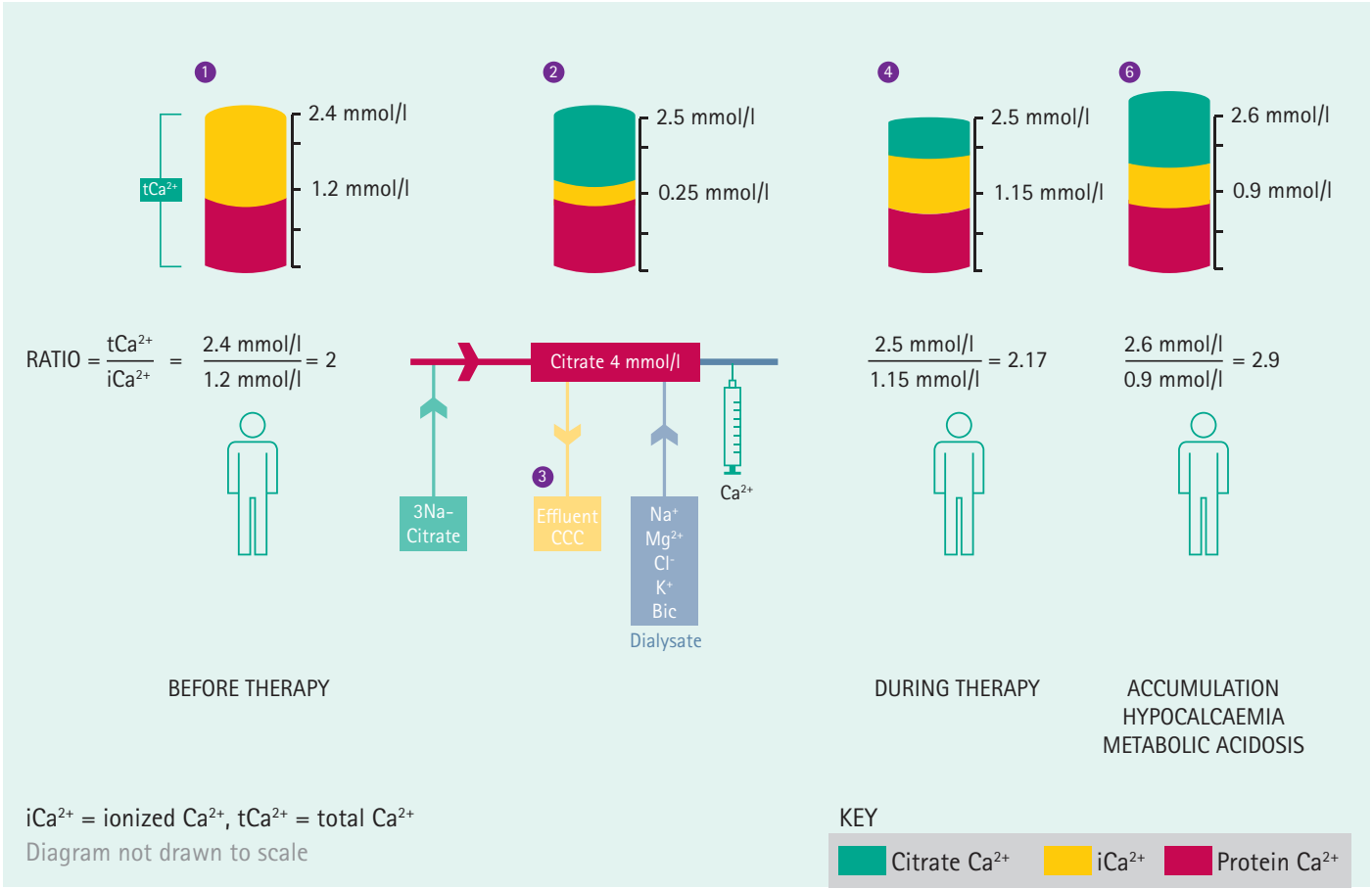
- Decrease blood flow and therefore decrease citrate volume
- Increase dialysate flow and therefore increase citrate clearance
- Anticipate that it can take four - six hours to see a change to the patients metabolic status after altering either blood flow or dialysate flow
- Generally speaking, if you do not see a significant improvement in pH or calcium ratio after six hours, do not delay, instead, switch to a different anticoagulant and continue CRRT for a minimum of four hours to clear the remaining citrate calcium complexes from the patient
- Always refer to your protocol for trust specific guidance on timings of interventions
- Some protocols may ask that you decrease your citrate dose based on your post filter ionized calcium level
- Bespoke management after discussion with the medical team is possible i.e., borderline accumulation with a calcium ratio of around 2.4 may allow more conservative management
- High calcium ratios well over 2.5 may require immediate change of anticoagulation and no titration of blood flow or dialysate flow
- Discussion with your senior medical team is vital given the potential danger associated with citrate accumulation



(Reference 10. Schneider, et al)

Recommended actions

Changes to calcium concentration throughout therapy in citrate accumulation



The above diagram is an example of citrate anticoagulation in CVVHD in a patient who is accumulating CCC

1. Prior to treatment, the patients iCa is 1.2 (the yellow wedge), their tCa is 2.4, so we can conclude their protein bound Ca is also 1.2 (the red wedge). The protein bound Ca is not interacting with citrate so the concentration shouldn't change much throughout RCA.

2. When 4 mmol citrate/l blood is added, iCa begins to chelate to citrate and form citrate calcium complexes. The iCa in the haemofilter reaches a concentration of 0.25. The remainder of the iCa is still present in the blood but it is now chelated to citrate (the green wedge). Protein bound calcium is unaffected.

3. Approximately 1/3 of the citrate calcium complexes are lost in the effluent and this is what is compensated for by the calcium substitution. The green wedge will be reduced by 1/3.

4. The blood that goes back to the patient contains 2/3 of the citrate calcium complexes, the iCa has been partially reoptimised based on the volume of effluent.

5. The expectation is that the citrate calcium complexes will be metabolized and all of the iCa chelated to the citrate will be released and therefore you will get a return to the status quo i.e. one.

6. Instead, the citrate calcium complexes are not broken down and so iCa is not released, there is no return to the status quo. Calcium substitution needs continue to increase and therefore the tCa starts to climb. In this example, tCa increases to 2.6 whilst iCa falls to 0.9. Calcium ratio is therefore 2.9.

Insufficient citrate load[10]

Calcium free bicarbonate solution and Mexsol contain a lower concentration of bicarbonate than Duosol as it is anticipated that the patient will produce bicarbonate via the metabolism of citrate. If the patient is receiving an inadequate volume of citrate, their ability to produce bicarbonate will be hampered and their buffering capacity will be affected. This can be seen in patients who become, or remain acidotic whilst on RCA. Crucially, systemic ionized calcium levels will be normal, there will be no additional demand for calcium substitution and the calcium ratio will also remain within normal limits.

In order to rectify this issue, increase the citrate volume by increasing the blood flow and decrease dialysate flow in order to decrease citrate clearance (in accordance with the trust protocol) and check the patients pH four - six hours later. Some protocols may also prompt you to increase the renal dose by increasing the dialysate flow. This will increase the rate of clearance which may also be beneficial in patients experiencing acidosis.

Important points

- Citrate flow adjusts automatically with blood flow
- Calcium must always be substituted via the integrated syringe, it is delivered on the venous line
- Calcium flow adjusts automatically with dialysate flow
- Dialysate must always be calcium free bicarbonate when using RCA

Start CVVHD with

4 mmol citrate/l of blood

1.7 mmol calcium/l of effluent

If you select the incorrect dialysate solution and it contains calcium, the concentration of calcium within the haemofilter will begin to climb. This may prompt you to increase your citrate dose if that is the trust practice. If you do not increase your citrate dose, it is highly probable that the circuit will clot. In addition to this, the patient will receive calcium substitution from both the calcium syringe and the dialysate bag, causing their systemic ionized calcium to become elevated. In turn, this will prompt you to decrease the calcium substitution dose.

You can only titrate your:

- Calcium dose from 0.2 - 3.0 mmol calcium/l effluent
- Citrate dose from 2.0 - 6.0 mmol citrate/l blood

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N.B The information included in this document is taken from available literature and internal B. Braun educational material (Susca, 2021) and is for guidance only. Please refer to your hospital physicians and the OMNI IFU for full use of the OMNI machine.

Notes

Notes

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