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A regional citrate anticoagulation protocol for pre-dilutional CVVHDf: The 'Modified Alabama Protocol'

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Summary
Background: The use of citrate to anticoagulate the Continuous Renal Replacement Therapy (CRRT) circuit has not been widely adopted in Australia as an alternative to heparin due to treatment complexity and risks of metabolic complications and availability of suitable solutions. However, interest persists in citrate anticoagulation as a viable alternative when heparin is either contraindicated or has failed to provide an adequate circuit lifespan due to dialyser clotting.
Aim: This paper will describe a regional citrate anticoagulation protocol based on the 'Alabama Protocol' (AP) for pre-dilutional continuous veno-venous haemodiafiltration (CVVHDf) adapted to meet local requirements of an Australian tertiary medical-surgical intensive care unit.
Discussion: The 'Modified Alabama Protocol' (MAP) uses base solutions which are now commercially available in Australia to produce a 0.5% citrate concentrate as the replacement fluid and a bicarbonate based, calcium-free solution as the dialysate. A number of additives are required to be added to the base solutions in order to match the requirements of the protocol. The anticoagulatory effects of citrate are monitored by reviewing simultaneous blood samples taken from the patient's arterial line and the post-dialyser sample port of the CRRT circuit. Post-dialyser and systemic ionised calcium levels in addition to the patient's base excess are easily obtainable by processing the blood samples through a blood gas analyser on site in

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the intensive care unit. Acid-base and electrolyte disturbances are controlled by adjusting the flow rate of replacement fluid and dialysate. As the protocol provides consistent directions on how to achieve desired biochemical values and when medical intervention is required, the approach offers an ideal opportunity for trained nursing staff to follow such a protocol at the bedside.
Conclusion: This paper describes a practical protocol for the delivery of regional citrate anticoagulation for pre-dilutional CVVHDf. The protocol maintains the flexibility in dialysis/haemofiltration dose prescription and advises on the requirement for monitoring and necessary adjustments to prevent the development of metabolic disturbances. This may assist regional citrate to achieve wider acceptance as an alternative anticoagulation strategy for critically ill patients.

1. Introduction

Continuous Renal Replacement Therapy (CRRT) is an established technique for the treatment of severe acute renal failure (ARF) in the critically ill patient.[1] A requirement, in most instances is, for some form of continuous circuit anticoagulation to sustain circuit life and obtain the maximum benefit from the treatment. The ability of Continuous Veno-Venous Haemofiltration (CVVH) to stabilise urea and creatinine plasma concentration was shown in one study to be affected when the duration of treatment received was less than 16 hr during a 24-hr cycle due to accumulative periods of circuit downtime.[2] In 2001, Silvester et al.[3] reported heparin was the anticoagulant most commonly used for CRRT in Australia despite the risks associated with its use. The incidence of haemorrhage and the development of heparin-induced thrombocytopaenia (HIT) has contributed to an increasing interest in the use of alternative agents and strategies to anticoagulate the CRRT circuit.[4]

The use of citrate to anticoagulate the CRRT circuit has been shown to be an effective alternative to heparin in a variety of different treatment modalities.[5–8] The development of protocols for citrate added to commercially available solutions has increased interest for how this approach to circuit management may be more widely applied. The 'Alabama Protocol' (AP) by Tolwani et al. [9] is designed to deliver citrate anticoagulation for continuous veno-venous haemodiafiltration (CVVHDf). The value of CVVHDf as a treatment modality is that it employs both diffusion and convection to maximise the range of molecules which are cleared, with one study suggesting the addition of a dialysis dose (diffusion) to haemofiltration increased patient survival.[10]

2. How citrate works

Citrate causes anticoagulation by a process referred to as chelation. An ionic bond is formed between citrate and calcium which reduces the amount of ionised calcium available for blood clotting. The chelation of ionised calcium (Ca_i^{2+}) by citrate is used to prevent coagulation in blood sample specimen tubes and in blood transfusion bags. Ionised calcium is required in several steps of the clotting cascade.[11] As shown in Fig. 1, the depletion of ionised calcium into non-ionised calcium-citrate complexes interrupts activation at several stages of the clotting cascade.

3. Why consider citrate?

Across Australia and in other regions of the world critically ill patients with severe ARF routinely receive CRRT in support of renal failure.[12] Low-dose heparin is commonly used to prolong the life of the CRRT circuit. In patients who are at high risk of bleeding or suspected of HIT heparin is withheld and an alternative agent and/or strategy selected. In our experience, alternative approaches when heparin is contraindicated are often less than satisfactory. For example, the use of pre-membrane heparin and post-membrane protamine to achieve 'regional' heparinisation can be associated with hypotension and careful monitoring of coagulation parameters required to ensure the dose of protamine is sufficient to antagonise post-dialyser heparin.[13,14] Prostacyclin has been shown to be a more expensive method to anticoagulate the circuit when compared with regional citrate anticoagulation[15] and is associated with vasodilatory effects leading to hypotension and

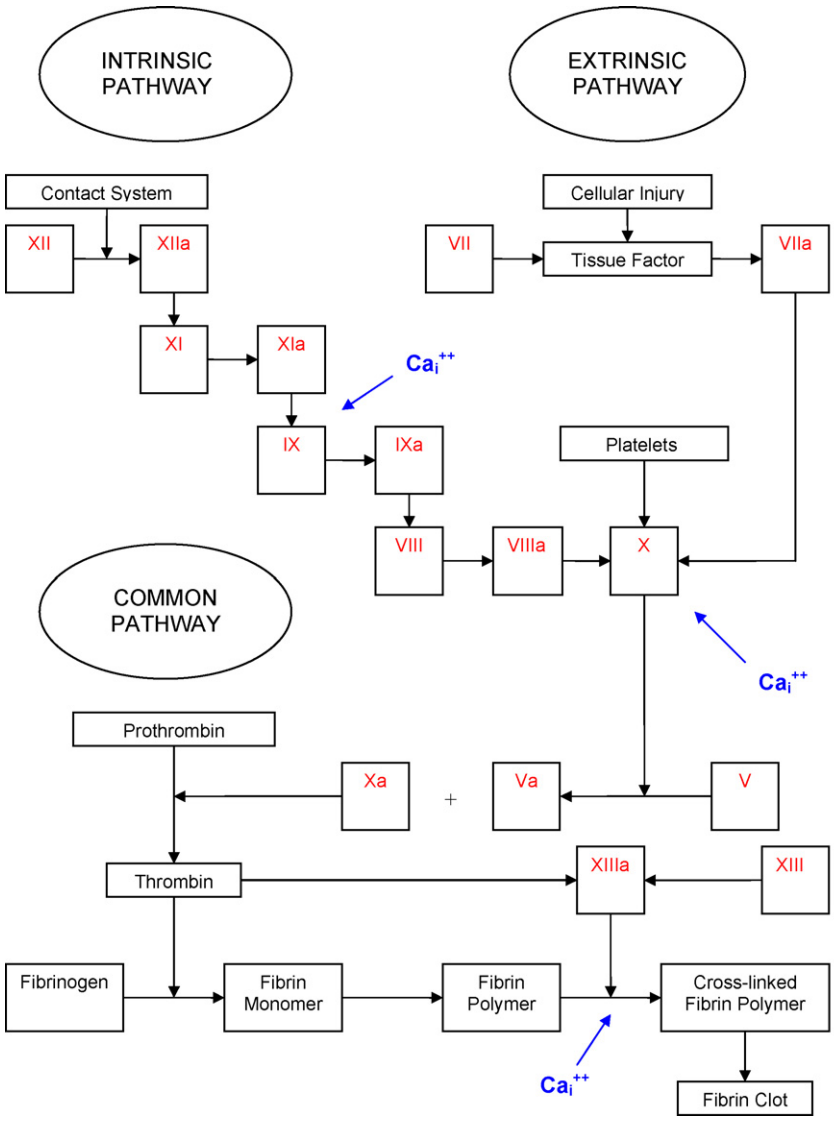

Figure 1 The blood coagulation cascade and the requirement for Ca_i^{2+}.[11]

pulmonary shunting causing hypoxaemia.[16] Danaparoid is an anticoagulant that requires specific factor Xa assays which are not measured in routine blood coagulation tests and the anticoagulatory effects are not easily reversed.[17] Anticoagulation-free CRRT works best when the patient has a severe coagulopathy.[18]

The benefit of citrate over heparin and other anticoagulation strategies is based on the ability to accurately control the anticoagulatory effect caused by the chelation of calcium to the CRRT circuit. Systemic anticoagulation is prevented by the infusion of calcium to prevent systemic ionised hypocalcaemia, clearance of citrate through the dialyser, and metabolism of citrate by the liver to bicarbonate also providing necessary buffer activity. This method provides an anticoagulation effect within the circuit and a reversal agent to normalise coagulation in the patient, known as 'regional anticoagulation' or in this case 'regional citrate'. The incidence of bleeding complications was significantly lower and circuit life longer when regional citrate was compared with systemic heparin in a randomised controlled study.[19] No difference in circuit life was observed during a randomised controlled crossover study when regional heparinisation was compared with regional citrate anticoagulation.[20] International experience suggests that regional citrate is a viable alternative anticoagulation strategy for CRRT.[12] A summary of indications and contraindications for regional citrate anticoagulation is shown in Table 1.

Table 1 Indications and contraindications for regional citrate anticoagulation

Indications	Contraindications
Patients at high risk of bleeding (surgery within the previous 24 hr)	Acute liver failure
Patients suspected of heparin-induced thrombocytopaenia	High volume haemofiltration > 50 mL/kg
Rapid clotting of the circuit when treated without anticoagulation or recurrent clotting occurs despite the use of heparin	High blood flow rates > 200 mL/min

4. The 'Alabama Protocol'

The AP is designed for the use of citrate in pre-dilutional CVVHDf to achieve anticoagulation of the CRRT circuit whilst allowing for a wide range of dialysis/haemofiltration dose prescriptions. This is able to be accomplished without the requirement to alter the basic composition of the replacement fluid and dialysate once treatment is commenced.[9] The action of citrate as a buffering agent after liver metabolism and the important role citrate plays in acid-base control is central to the management of the protocol. Metabolic control and fluid balance is achieved by adjusting the flow rates of the replacement fluid and dialysate. At the same time the anticoagulatory effect of citrate on ionised calcium is maintained as blood travels through the circuit. The method of citrate delivery for pre-dilutional CVVHDf differs from other protocols. Instead of a concentrated single infusion the AP requires citrate to be placed in the replacement fluid.[6,21] The AP allows greater flexibility in the dose of dialysis and haemofiltration able to be delivered, and in the adjustments to the rate of blood flow able to be set when comparisons are made with other protocols.[22,23] Recent evidence suggests the survival of patients with ARF is improved when the intensity of renal replacement therapy is increased.[24,25] A summary of the main features of the 'Alabama Protocol' is given in Table 2.

Table 2 A summary of the main features of the 'Alabama Protocol'

- Citrate does not require direct measurement. Instead the effects of citrate can be measured indirectly by recording post-dialyser and systemic Ca_i^{2+} levels, monitoring blood pH, base excess and anion gap from arterial blood gases, and calculating the gap between systemic Ca_i^{2+} and Ca_{total}^{2+} levels. Unless otherwise indicated in the protocol these measurements can be taken to coincide with routine blood samples.
- The protocol is designed to allow the bedside nurse to make adjustments to account for changes in blood base excess and electrolytes. Alterations are made to the flow rate of replacement fluid and dialysate solution to maintain values within a specific range whilst ensuring the desired level of circuit anticoagulation is maintained.
- The ability of CVVHDf mode to remove a broad range of solutes by diffusion and convection is maintained. Adjustments can be made to the dose of dialysis or haemofiltration required. Solute clearance is not constrained by narrow limitations placed on the rate of blood flow.

The 'Modified Alabama Protocol' (MAP) is an adaptation of the original AP to meet the requirements of an Australian tertiary medical-surgical Intensive Care Unit (ICU). The adaptations include:

1. minor differences in the composition of the replacement and dialysate solutions to comply with commercially available base solutions,
2. minor variations in the set-up and operation of CVVHDf,
3. the use of a concentrated calcium gluconate infusion, and
4. differences on the range of metabolic parameters used to monitor the effects of citrate.

5. Nursing responsibilities

Once a medical decision is made to use citrate the request is charted using the '*Bedside Modified Alabama Protocol for 0.5% Citrate in CRRT (Prescription Orders)*' document as shown in Table 3. Detailed instructions are provided on the prescription sheet as to additives which are required to be injected into the base solutions. Important parameters obtained from blood samples are recorded on the back of the '*Bedside Modified Alabama Protocol for 0.5% Citrate in CRRT (Blood Results)*' document as shown in Table 4. This document provides a set of parameters which direct the nurse how to maintain values within a specific range and a set of instructions to 'trouble shoot' measurements when they are outside the desired range of values.

Table 3 The bedside 'Modified Alabama Protocol' for 0.5% citrate in CRRT (prescription orders)

Patient Label

Bedside 'Modified Alabama Protocol' for 0.5% Citrate in CRRT

Date & Time	Dr Sign	Replacement Fluid Edwards Lifesciences™ Citrate 14mmol/L Blue Label 5L Bag	Replacement Fluid Rate 1000-2000 (mL/hr)	Dialysate Edwards Lifescieneces™ Hemofiltration Fluid No Calcium Green Label 5L Bag	Dialysate Rate 1000-2500 (mL/hr)	Post-dialyser Replacement Fluid (HFRF 5L Bag, Baxter™)	Balance	Nurse Sign
		Add: 200mL ACD-A		**Add:** 100mL 8.4% $NaHCO_3$ 20mL 20% NaCl		**200mL/hr**		
		Add: 200mL ACD-A		**Add:** 100mL 8.4% $NaHCO_3$ 20mL 20% NaCl		**200mL/hr**		
		Add: 200mL ACD-A		**Add:** 100mL 8.4% $NaHCO_3$ 20mL 20% NaCl		**200mL/hr**		
		Add: 200mL ACD-A		**Add:** 100mL 8.4% $NaHCO_3$ 20mL 20% NaCl		**200mL/hr**		
		Add: 200mL ACD-A		**Add:** 100mL 8.4% $NaHCO_3$ 20mL 20% NaCl		**200mL/hr**		

ACD-A = Acid Citrate Dextrose A
Ca_i^{++} = ionised calcium
Ca_{TOTAL}^{++} = total calcium
HIT = heparin-induced thrombocytopaenia
BE = base excess

Mode: CVVHDf

- Calculate the total dose required (mL/kg/hr)
- Subtract 200mL required as post-dialyser replacement fluid
- Initiate the remaining pre-dialyser replacement fluid/dialysate at 1:1 ratio

Blood Flow

- 120-170mL/hr (initiate at 150mL/hr)

Prime circuit with heparin (optional) unless HIT

10% Calcium Gluconate Infusion (5g/50mL) via separate central line

- 50mL of undiluted 10% calcium gluconate attached to the Prismaflex™ syringe driver
- Initiate at 10mL/hr for first dialyser (Ca_i^{++} < 1.1mmol/L) or 8mL/hr (Ca_i^{++} > 1.1mmol/L) or at rate used for previous dialyser

Record Ca_i^{++}/BE 1 hour after initiation or any change in prescription then 6 hourly once stable

Report to Medical Officer if:

- Base excess < -5 or > +5
- Ca_i^{++} < 0.9mmol/L or > 1.2mmol/L

Table 4 The bedside ''Modified Alabama Protocol'' for 0.5% citrate in CRRT (blood results)

Date	Time	Post-dialyser Ca_i^{++}	Ca_{TOTAL}^{++}	Systemic Ca_i^{++}	Systemic Base Excess	Action
		0.2 - 0.4 mmol/L		0.9 - 1.2 mmol/L	-5 to +5	Desired Levels
						Baseline Results

Dialyser Clotting

- Check post-dialyser Ca_i^{++} (port on blue lumen) If post-dialyser Ca_i^{++} > 0.4mmol/L:
- ↓ 10% calcium gluconate by 1.5mL/hr when systemic Ca_i^{++} > 1.1mmol/L

OR

- ↑ 0.5% citrate solution by 100mL/hr when systemic Ca_i^{++} < 1.1mmol/L
- ↓ no calcium dialysate rate by 100mL/hr
- Recheck post-dialyser Ca_i^{++} in 1hr

A post-dialyser Ca_i^{++} < 0.2mmol/L corresponds to an extended clotting time:

- ↓ 0.5% citrate solution rate by 100mL/hr

Hypocalcaemia (systemic Ca_i^{++} < 0.9mmol/L)

- Systemic Ca_i^{++} 0.8 - 0.9mmol/L ↑ 10% calcium gluconate infusion by 1.5mL/hr
- Systemic Ca_i^{++} < 0.8mmol/L ↑ 10% calcium gluconate infusion by 3mL/hr and exclude citrate accumulation
- Recheck systemic Ca_i^{++} in 1 hr

Hypercalcaemia (systemic Ca_i^{++} > 1.2mmol/L)

- ↓ 10% calcium gluconate infusion by 1.5mL/hr

Metabolic Alkalosis (pH > 7.50, ↑ BE)

- Do not change concentration of base solutions
- ↑ no calcium dialysate rate by 100mL/hr
- ↓ 0.5% citrate solution rate by 100mL/hr

Metabolic Acidosis (pH < 7.30, ↓ BE)

- Do not change concentrations of base solutions
- Exclude citrate accumulation
- ↓ no calcium dialysate rate by 100mL/hr
- ↑ 0.5% citrate solution rate by 100mL/hr

Citrate Accumulation

- Falling pH/BE and increasing anion gap
- Calcium Gap(Ca_{TOTAL}^{++} minus Ca_i^{++}) > 1.6mmol/L
- Direct measurement of citrate is unnecessary

Management involves:

- ↓ 0.5% citrate solution rate by 100-200mL/hr
- ↑ no calcium dialysate rate by 100-200mL/hr
- Recheck Ca_i^{++}/Ca_{TOTAL}^{++}/pH/BE in 1hr
- Consider alternative anticoagulant

6. Solutions

At present there are no commercially available solutions in Australia that exactly match the regime set out by Tolwani et al. [9] as the AP. The MAP uses a commercially available 5000 mL bag as replacement fluid with a base solution comprising of 14 mmol/L of citrate, 140 mmol/L of sodium, 99 mmol/L of chloride and 1 mmol/L of potassium (AHK6022 haemofiltration solution citrate 14 mmol/L, Edwards Lifesciences™, Toongabbie NSW) and a commercially available 5000 mL bag as dialysate with a base solution comprising of acetate 4.5 mmol/L as the alkali component, 110 mmol/L of sodium, 99 mmol/L of chloride, 1 mmol/L of potassium, 0.75 mmol/L of magnesium and 10 mmol/L of glucose (AHK6031 haemofiltration replacement fluid-no calcium, Edwards Lifesciences™, Toongabbie NSW). In the replacement fluid 200 mL of commercially available anticoagulant citrate dextrose solution formula A (ACDA-A) comprising of 112 mmol/500 mL of sodium, 56.5 mmol/500 mL of citrate and 2.45% of dextrose is added increasing the concentration of citrate to 17.8 mmol/L and sodium to 143 mmol/L (AHB7898 ACDA-A 500 mL bag, Baxter™, Toongabbie NSW). This equates to a 0.5% citrate solution when the number of grams is expressed as a percentage. To the dialysate 100 mL of 8.4% $NaHCO_3$ (100 mmol) is added to give a final alkaline concentration equivalent to 24.0 mmol/L HCO_3 and 20 mL of 20% NaCl (78 mmol) to give a final Na^+ concentration of 142 mmol/L. Both bags can be modified by the nurse at the bedside. Other electrolytes such as potassium and phosphate are added as required to both bags but no calcium. A 50 mL syringe of neat 10% calcium gluconate (2.2 mmol/10 mL) is prepared as a continuous infusion to replace the calcium lost as chelated

Table 5 Edwards Lifesciences™ base solutions and minor modifications required to comply with the 'Modified Alabama Protocol' for pre-dilutional CVVHDf

Replacement fluid (citrate 14 mmol/l) blue label 5 L bag		
Citrate	70 mmol	(14 mmol/L)
Na^+	700 mmol	(140 mmol/L)
Cl^-	495 mmol	(99 mmol/L)
K^+	5 mmol	(1 mmol/L)
ACD-A 500 mL bag		
Citrate	56.5 mmol	(11.3 mmol/100 mL)
Na^+	112 mmol	(22.4 mmol/100 mL)
Dextrose	2.45%	
Add 200 mL ACD-A to Blue Label 5 L Bag		
Citrate	22.6 mmol	
Na^+	44.8 mmol	
Final concentration of citrate and Na^+ in replacement fluid blue label 5 L bag		
Citrate		17.8 mmol/L
Na^+		143.2 mmol/L
Dialysate — hemofiltration fluid (no calcium) green label 5 L bag		
Acetate (equimolar equivalent to bicarbonate)	22.5 mmol	(4.5 mmol/L)
Na^+	550 mmol	(110 mmol/L)
Cl^-	540 mmol	(108 mmol/L)
K^+	5 mmol	(1 mmol/L)
Mg^{2+}	3.75 mmol	(0.75 mmol/L)
Glucose	50 mmol	(10 mmol/L)
Add 100 mL 8.4% $NaHCO_3$		
$HC0_3$	100 mmol	
Na^+	100 mmol	
Add 20 mL 20% NaCl		
Na^+	78 mmol	
Final concentration of HCO_3 and Na^+ in dialysate — hemofiltration fluid (no calcium) green label 5 L bag		
$HC0_3$		23.9 mmol/L
Na^+		142.2 mmol/L

Table 6 Gambro™ base solutions and minor modifications required to comply with the 'Modified Alabama Protocol' for pre-dilutional CVVHDf

Prismocitrate 10/2 5 L bag		
Trisodium citrate	50 mmol	(10 mmol/L)
Citrate acid	10 mmol	(2 mmol/L)
Na^+	680 mmol	(136 mmol/L)
Cl^-	530 mmol	(106 mmol/L)
K^+	0 mmol	(0 mmol/L)
Add 300 mL ACD-A to prismocitrate 10/2 5 L bag		
Trisodium Citrate	28 mmol	
Citrate Acid	10 mmol	
Na^+	67.2 mmol	
Final concentration of trisodium citrate, citrate acid and Na^+ in prismocitrate 10/2 5 L bag		
Trisodium citrate		14.7 mmol/L
Citrate acid		3.8 mmol/L
Na^+		141 mmol/L
Prismocal 5 L bag (no additional additives required)		
Bicarbonate	160 mmol	(32 mmol/L)
Lactate	15 mmol	(3 mmol/L)
Na^+	700 mmol	(140 mmol/L)
Cl^-	530 mmol	(106 mmol/L)
K^+	0 mmol	(0 mmol/L)
Mg^{2+}	2.5 mmol	(0.5 mmol/L)
Glucose	0 mmol	(0 mmol/L)

calcium-citrate complexes through the dialyser. Calcium chloride is not used due to a higher salt content compared with calcium gluconate and the increased risk of tissue necrosis should extravasation occur.[26] A summary of Edwards Lifesciences™ base solutions and modifications necessary to meet fluid composition requirements of the protocol is shown in Table 5. The MAP can also be used with other commercially available base solutions such as those manufactured by Gambro™ as shown in Table 6.

7. Setup of the circuit

The MAP is suitable for use with CRRT circuits and machines which are capable of delivering replacement fluid at the vascular access site when blood first leaves the body. Similar to other CRRT machines the same number of infusions are required using the Prismaflex™ (Hospal, Lyon, France) to deliver regional citrate anticoagulation for pre-dilutional CVVHDf as is used for low-dose heparin (replacement fluid, dialysate and anticoagulant). The setup of the circuit is shown in Fig. 2. The replacement fluid bag containing the citrate is attached to the pre-blood pump line to maximise the effect of citrate as blood travels along the circuit. The calcium gluconate infusion is delivered using the syringe driver located on the Prismaflex™ (normally used to administer heparin) through a separate central line and not through the circuit by the attachment of extension tubing to the syringe. This reduces the risk of overdosing the patient with calcium by ensuring the syringe is taken down at the same time as the rest of the circuit.

The MAP permits pre-dilutional CVVHDf to operate under a broad range of settings according to the dose of dialysis and haemofiltration required. The replacement fluid can be set between 1000 and 2000 mL/hr and the dialysate at between 1000 and 2500 mL/hr (effluent range 2000—4500 mL/hr). The ratio between the infusions on commencement of treatment should be at the same rates with subsequent changes in the volume of fluid exchanges only made according to the patient's blood results and the range of values specified in the protocol. The blood flow rate is initially set at 150 mL/min but can be adjusted to operate between 120 and 170 mL/min. The calcium gluconate infusion is commenced at 10 mL/h ($Ca_i^{2+} < 1.1$ mmol/L) or 8 mL/hr ($Ca_i^{2+} > 1.1$ mmol/L) for the first dialyser or continued at the same delivery rate as was used for the previous dialyser.

The option provided by the Prismaflex™ to access the replacement fluid pump line and deliver fluid post-dialyser can be used to reduce the blood/air interface and the potential for blood clot-

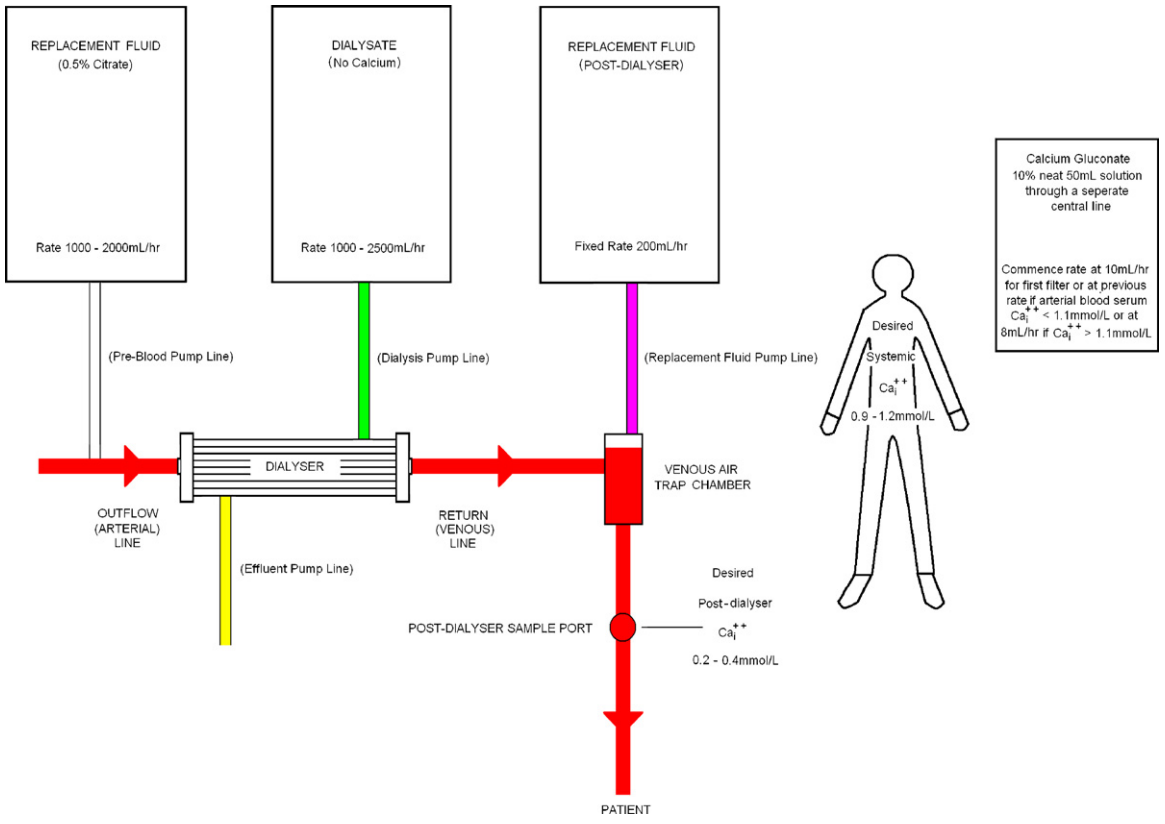

Figure 2 'Modified Alabama Protocol' setup for 0.5% citrate in pre-dilutional CVVHDf.

ting in the venous air trap chamber. We suggest 200 mL/hr of replacement fluid (AHB7864 haemofiltration replacement fluid 5000 mL bag, Baxter™, Toongabbie NSW) is delivered post-dialyser. In choosing this option the volume of fluid delivered post-dialyser (200 mL) is first subtracted from the required dialysis/haemofiltration dose. The remaining volume is then divided equally between the replacement fluid and dialysate and set at the same rate of flow.

8. Monitoring

The effects of citrate can be monitored by the measurement of Ca_i^{2+} levels from arterial blood and post-dialyser venous blood gas results and total calcium (Ca_{total}^{2+}) blood serum levels. A set of baseline measurements is initially required to be taken prior to commencement of treatment. Once the circuit has been operating for 1 hr a post-dialyser venous blood gas sample for Ca_i^{2+} levels and a systemic arterial blood gas to monitor the systemic Ca_i^{2+} and base excess should be recorded. Unless the results obtained are outside the protocol's range of values or changes have been made to previous settings further blood sampling every 6 hr is considered adequate. The use of an arterial blood gas machine located in the ICU can greatly facilitate the speed whereby the bedside nurse can monitor post-dialyser and systemic Ca_i^{2+} levels. The requirement for twice daily Ca_{total}^{2+} levels can be incorporated with other requests which require blood samples to be sent to the laboratory for analysis thereby minimising blood loss due to additional sampling.[27] The desired range of Ca_i^{2+} levels for post-dialyser and systemic blood samples is shown in Fig. 2.

9. Trouble shooting

The MAP requires specific interventions to be followed to prevent the development of metabolic disturbances associated with the use of citrate. This protocol advises on what adjustments are necessary and specifies a range of values designed to minimise the development of metabolic alkalosis (excessive citrate), metabolic acidosis (inadequate citrate metabolism), hypocalcaemia (inadequate calcium infusion dose) and hypercalcaemia (excessive calcium infusion dose). In an attempt to

maintain simplicity and safety, all changes to infusion rates are made in 100 mL/hr increments for the replacement and dialysate solutions and 1.5 mL/hr increments for the calcium gluconate infusion.

9.1. Metabolic alkalosis

As each molecule of citrate is rapidly metabolised to three molecules of bicarbonate, the continuous infusion of 0.5% citrate places the patient at risk of developing a metabolic alkalosis. Since critically ill patients are subject to fluctuations in pH the patient's base excess is used to monitor metabolic variations in acid-base caused by renal replacement therapy. A base excess that is elevated above +5 requires the dialysate flow rate to be increased by 100 mL/hr and a corresponding decrease in the flow rate of the 0.5% citrate replacement fluid by 100 mL/hr. This action will reduce the amount of base delivered to the patient. The base excess is repeated each hour until the base excess drops to the acceptable range of values specified in the protocol.

9.2. Metabolic acidosis

Persisting or worsening metabolic acidosis may present due to the underlying disease process reducing liver function and/or the onset of organ ischaemia, inadequate dialysis clearance, and the accumulation of free citrate ions. If no new explanation is identified, the dialysate flow rate should be decreased by 100 mL/hr followed by a corresponding increase in the 0.5% citrate replacement volume of 100 mL/hr. This is repeated each hour until a base excess is maintained above −5. Increasing the rate of fluid replacement allows more citrate to be delivered through the circuit and metabolised to bicarbonate in the body. This increases the availability of alkali and adjusts the pH level away from being acidic.

9.3. Hypocalcaemia

Systemic ionised hypocalcaemia can occur for two main reasons. Most commonly calcium is lost through the dialyser by the processes of convection and diffusion. Second, ionised hypocalcaemia can occur with the systemic accumulation of citrate in the blood (see citrate accumulation section). This second scenario usually occurs in the setting of hepatic dysfunction, especially acute liver failure. Adjustments are made to the calcium gluconate infusion and increased by 1.5 mL/hr when the systemic level of Ca_i^{2+} is between 0.8 and 0.9 mmol/L, or the infusion is increased by 3 mL/hr should the systemic level of Ca_i^{2+} be 0.8 mmol/L. The incremental increase in the calcium gluconate infusion continues until a systemic ionised calcium level of >0.9 mmol/L is reached.

9.4. Hypercalcaemia

Rarely, the requirement for a continuous calcium gluconate infusion may result in the development of hypercalcaemia. When systemic Ca_i^{2+} levels are >1.2 mmol/L adjustments should be made to decrease the calcium gluconate infusion by 1.5 mL/hr until a systemic Ca_i^{2+} level of <1.2 mmol/L is reached.

9.5. Dialyser clotting

Monitoring the degree of anticoagulation within the extracorporeal circuit is achieved by measuring the Ca_i^{2+} level in the post-dialyser blood just before it is returned to the patient. A post-dialyser blood sample showing a Ca_i^{2+} level >0.4 mmol/L suggests the level of citrate in the blood may be insufficient to anticoagulate the circuit. This may result in premature clotting and shorten the lifespan of the circuit. To increase the anticoagulatory effect within the circuit when the systemic Ca_i^{2+} level is >1.1 mmol/L the calcium gluconate infusion should be decreased by 1.5 mL/hr. If the systemic Ca_i^{2+} level is <1.1 mmol/L the rate of 0.5% citrate replacement fluid should be increased by 100 mL/hr to make more citrate available to mix with the blood and chelate ionised calcium. This can be combined with a reduction in the rate of dialysate by 100 mL/hr to lessen the amount of non-ionised calcium in the form of calcium-citrate molecules transported out of the blood and across the membrane. A post-dialyser blood sample taken 1 hr after adjustments have been made will determine if further changes are necessary to achieve a post-dialyser Ca_i^{2+} blood level <0.4 mmol/L. The post-dialyser Ca_i^{2+} blood sample should be maintained between 0.2 and 0.4 mmol/L. A post-dialyser blood sample showing a Ca_i^{2+} <0.2 mmol/L corresponds to an extended clotting time. This can be corrected by decreasing the rate 0.5% citrate replacement fluid by 100 mL/hr.

9.6. Citrate accumulation

The accumulation of citrate can occur when metabolism by the liver is poor and/or there is a reduction in clearance of citrate through the dialyser. This causes the number of calcium-citrate molecules to accumulate in the body. When this

happens, the non-ionised calcium level contributes to a significant increase in the total serum calcium level. This causes an increase in the difference between the total serum calcium and the serum-ionised calcium (the 'calcium gap'). The detection of citrate accumulation does not require a direct measurement of blood citrate levels but is able to be detected by calculating the 'calcium gap' between systemic Ca_i^{2+} and Ca_{total}^{2+}. Indications of an excessive amount of citrate in the body can be suspected when the following scenarios arise:

- falling pH/base excess,
- increasing difficulty in maintaining a post-dialyser Ca_i^{2+} blood sample level <0.4 mmol/L,
- increasing difficulty in maintaining a systemic Ca_i^{2+} blood sample level >0.9 mmol/L,
- increasing anion gap, and
- increasing calcium gap (Ca_{total}^{2+} minus Ca_i^{2+}) >1.6 mmol/L.

Management of these derangements should consider decreasing the rate of 0.5% citrate replacement fluid by 100—200 mL/hr and increasing the dialysate by a similar amount to remove more non-ionised calcium-citrate complexes from the blood. After 1 hr recheck Ca_{total}^{2+} levels to determine whether the calcium gap has been reduced. Repeat arterial blood gases to observe for an increase in blood pH/base excess and a decrease in anion gap. Measure the post-dialyser blood sample and aim for a Ca_i^{2+} level <0.4 mmol.

9.7. Other metabolic considerations

The use of a dilute citrate concentrate with the sodium (Na^+) content low in the replacement fluid reduces the possibility of hypernatremia which has been a complication reported in other protocols using a concentrated trisodium citrate solution.[6] Hypomagnesaemia has also been observed due to the chelation of magnesium (Mg^{2+}) during regional citrate anticoagulation.[28] The monitoring of Na^+ and Mg^{2+} serum levels is not referred to directly in the protocol but measurements are part of routine blood sampling and abnormalities should be corrected as required.

10. Conclusions

The use of regional citrate for CRRT can provide an alternative anticoagulation strategy. Although the incidence of HIT is eliminated and the risk of systemic bleeding is reduced, the use of citrate increases the complexity of CVVHDf. The possibility of metabolic complications require blood pH and electrolytes to be closely monitored and customised replacement fluids/dialysate solutions increase the potential for drug errors to occur during fluid preparation.

The MAP is an adaptation of the original AP developed by Tolwani et al., [9] which is suitable for clinical use and practical to implement in an Australian tertiary medical-surgical ICU. The protocol allows regional anticoagulation for CVVHDf to be delivered using citrate which does not place restrictions on the operational efficiency of the treatment and at the same time minimising the possibility of metabolic side-effects. Our experience of using this protocol supports the view that regional citrate is an effective anticoagulation strategy for patients at high risk of bleeding or suspected of HIT. As confidence with regional citrate anticoagulation grows, it may also emerge as an alternative to heparin in situations where treatment is frequently interrupted by early clotting of the circuit.

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Chest X-ray quiz

Compiled by Marea Reading, CNC, St Vincent's Hospital, Sydney Australia

Question

This is an anterior to posterior (AP) erect chest X-ray of a 57 year old lady following cardiac surgery via medium sternotomy to replace her mitral valve. You are asked to comment on the location of the central line and pulmonary artery catheter. Is there a problem following the subclavian placement of these lines? Also comment on the lung fields.

For answer and discussion turn to page 171 of this issue.