Continuous Renal Replacement Therapy (CRRT) with citrate anticoagulation; The Kalmar protocol

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Introduction

AKI (Acute Kidney Injury) is commonly occurring in ICU patients, as part of multi organ failure.

AKI is a common (8-16% of hospital admissions) and serious condition with a fourfold increase in hospital mortality (1,2) and there is a rising incidence of AKI over time (3).

The incidence of AKI ranges from 16% in a cardiac surgery population to 35.8% in a mixed ICU (4)

Various forms of RRT (Renal Replacement Therapy) have over the past decades been used to treat this patient category.

The use of RRT in ICU patients is internationally applied in 8-10% of ICU patients and its use is steadily going up by approximately 10% per year (8-12).

CRRT (Continuous Renal Replacement Therapy), first described in 1968, has emerged as the preferable technique over IRRT (Intermittent Renal Replacement Therapy).

CRRT has not been proven to have any survival benefits over IRRT in the ICU setting, but the chance for renal recovery is significantly better with CRRT and also the chance for dialysis independency vs IRRT. The hazard ratio is 0.75 (5,6).

Considering the above and that the yearly mortality in patients on chronic hemodialysis is high (18.2% in Sweden) one can clearly see that CRRT has a mortality benefit over IRRT (7).

Anticoagulation in CRRT

KDIGO states:

"We recommend using anticoagulation during RRT in AKI" (13).

Anticoagulation is used to prevent clotting of the filter, which increasingly leads to reduced solute clearance and thereby reduced effectiveness, shorter filter survival and increased downtime.

Historically unfractionated heparin has been the major mean to achieve anticoagulation in CRRT. Other means of anticoagulation includes the use of LMWH, surface treated filters with heparin binding sites, prostacyclin, thrombin antagonists and others.

The downside of heparin and heparin analogues have been bleeding complications (common) and HIT (rare).

In this light, citrate has emerged as the better and preferable method of anticoagulation and KDIGO also states: "For anticoagulation in CRRT, we suggest using regional citrate anticoagulation rather than heparin in patients who do not have contraindications for citrate" (13).

The use of citrate, compared to heparin, results in less bleeding complications and better filter survival and thereby less nurse- and doctor workload (14-15).

Regional citrate anticoagulation (RCA)

In RCA, sodium citrate is infused pre filter in the extracorporeal circuit, chelating ionized calcium to a calcium-citrate complex which lowers the ionized calcium concentration in the extracorporeal circuit and thereby inhibits clotting. The anticoagulative properties of citrate increases with increased blood concentrations of citrate and at 4 mmol/l the blood can no longer coagulate.

A calcium free dialysate solution should be used, not to counteract the anticoagulative activity of the citrate.

The major part of the calcium-citrate complexes are removed across the filter by diffusion and convection. The remaining calcium-citrate complexes are returned to the patient's bloodstream and are metabolized to citric acid and bicarbonate in the liver.

To compensate for the calcium losses over the filter, a systemic calcium infusion is required to maintain normal levels of ionized calcium in the patient's blood.

In the Prismaflex/Prismax (Baxter Healthcare Corporation, Chicago, IL, USA) CRRT machine, the calcium infusion dosage is regulated using an algorithm for calcium compensation. 100% calcium compensation means that 100% of the calculated calcium losses are compensated for. The range of calcium compensation is 30-200%.

Magnesium losses can also be significant in citrate anticoagulation, due to the formation of citrate-magnesium complexes and magnesium supplementation is often required, rarely above 20 mmol/day.

CRRT machines should, in our opinion, have the option of varying the citrate concentration. This gives the treating physician the possibility to minimize the citrate load on the liver, where citrate is metabolized, and provides a tool to affect the acid-base balance which will be described later.

In summary:

- A variable dose of citrate is infused pre filter to achieve ionized PF-calcium levels (post filter calcium) of 0.25-0.4 mmol/l. This will provide excellent anticoagulation of the extracorporeal circuit.
- A systemic infusion of calcium is provided to maintain ionized calcium levels of 1.0-1.2 mmol/l in the patient´s bloodstream.

Objectives behind the protocol

The main objectives of The Kalmar protocol are:

- CVVHDF-modality.
- To use a calcium free dialysate (Biphozyl).
- To obtain sufficient extracorporeal anticoagulation, using citrate (Regiocit).
- To use the lowest citrate dose possible to obtain sufficient anticoagulation, by monitoring PF-calcium levels with a goal of 0.25-0.4 mmol/l. The starting citrate dose is always 3.0 mmol/l.
- To maintain adequate ionized calcium levels in the patient`s blood by adjusting the calcium compensation level to a goal of 1.0-1,2 mmol/l.
- To enable control of the patient`s metabolic aspects of the acid-base balance by varying the citrate dose (citrate is metabolized to bicarbonate) and the dialysate flow (the higher the more bicarbonate losses and vice versa).
- To enable detection of citrate accumulation by monitoring calcium compensation levels and ionized calcium concentrations.
- To ensure an adequate dialysis dose/effluent flow that compensates for a calculated daily downtime of 15% (16-18).

The Kalmar protocol:

Settings according to the patients adjusted bodyweight using a citrate dose of 3.0 mmol/l and calcium compensation of 100%.

Weigh kg	Bloodflow ml/min	Dialysate ml/h	Citrate flow ml/h Pre-filter replacement (automatically adjusted by the monitior)	Replacement fluid post-filter ml/h	Results in an adjusted dialysis dose of: (15% downtime used in the calculation)
50	100	1 000	1000	200	37 ml/kg/h
60	110	1 100	1100	400	37 ml/kg/h
70	120	1 200	1200	500	35 ml/kg/h
80	130	1 300	1300	500	33 ml/kg/h
90	140	1 400	1400	500	31 ml/kg/h
100	150	1 500	1500	600	31 ml/kg/h
110	160	1 600	1600	700	30 ml/kg/h
120	170	1 700	1700	800	30 ml/kg/h
130	180	1 800	1800	1 000	30 ml/kg/h

Treatment flowchart
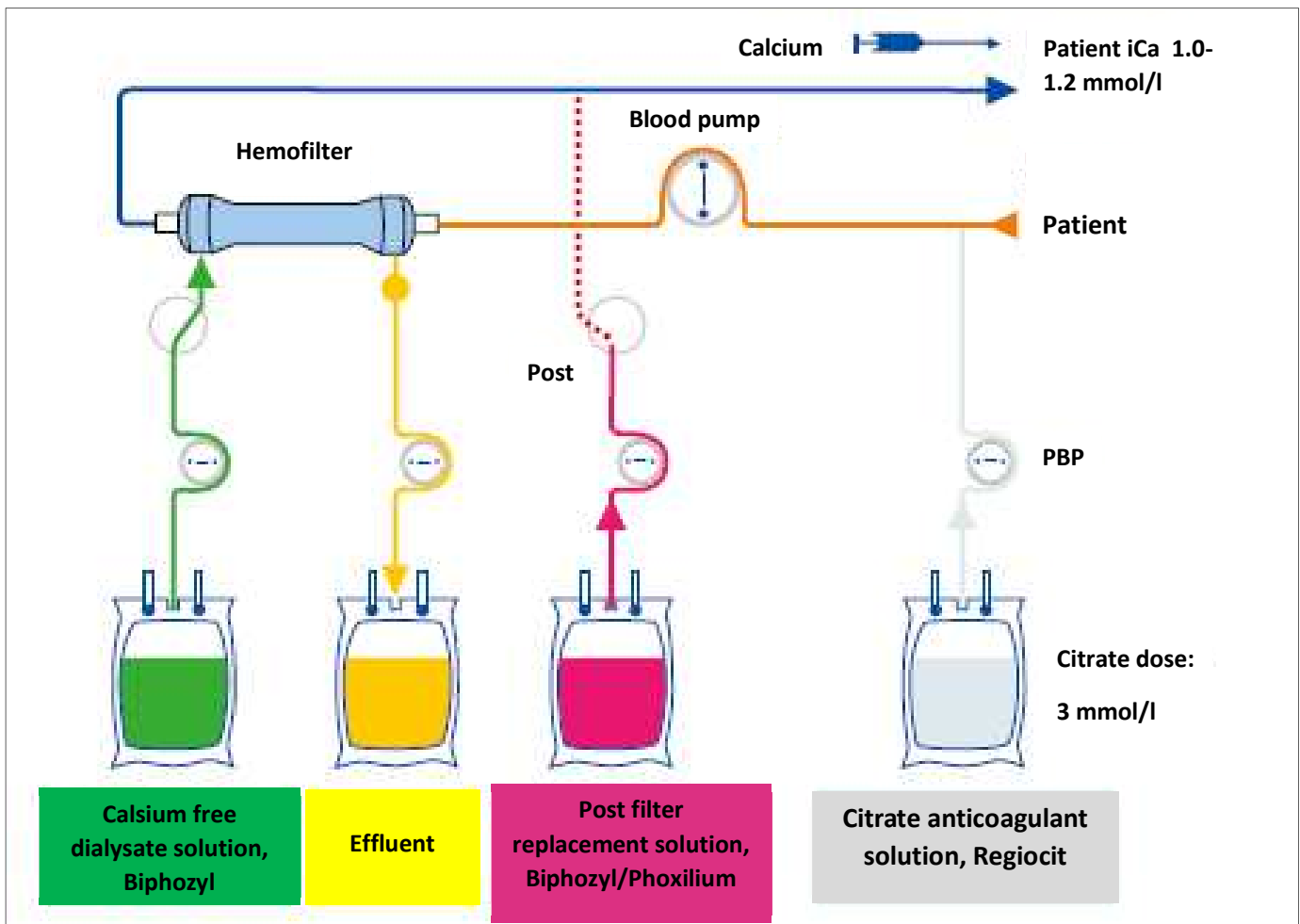
Citrate dose, post filter calcium and calcium homeostasis

In general, the post filter calcium levels provide information on the adequacy of the citrate dose. The level of ionized calcium in the patient`s blood provides information on the adequacy of the calcium compensation.

If post filter calcium is too low, the citrate dose is lowered in steps of 0.2-0.5 mmol/l.

If post filter calcium is too high, the citrate dose is increased in steps of 0.2-0.5 mmol/l.

Keep in mind that both of these actions also will affect the amount of bicarbonate produced by citrate metabolization.

If the ionized calcium in the patients' blood is <1.0 mmol/l, the calcium compensation should be increased by 5-10%, for example from 100% to 110%.
If the concentration is < 0,8 mmol/l a bolus dose of calcium should also be given.

We use the following table as a guideline for changes in citrate dose and calcium compensation:

	High PF-Ca	Normal PF-Ca	Low PF-Ca
Low Ionized P-Ca	**Increase citrate dose by 0,2 – 0,5 mmol/l** **Increase calcium compensation by 5-10%**	**Increase calcium compensation by 5-10%**	**Decrease citrate dose by 0,2 - 0,5mmol/l**
Normal Ionized P-ca	**Increase citrate dose by 0,2 – 0,5 mmol/l**		**Decrease citrate dose by 0,2 - 0,5 mmol/l**
High Ionized P-Ca	**Decrease calcium compensation by 5-10%**	**Decrease calcium compensation by 5-10%**	**Decrease citrate dose by 0,2 - 0,5mmol/l** **Decrease calcium compensation by 5-10%**

Citrate metabolism and accumulation

- Citrate is metabolized to citric acid in the liver, which generates bicarbonate.

- Each mmol of citrate generates 3 mmol of bicarbonate.

- Citrate can by this process be used as an indirect buffer.

- The citric acid, also generated in citrate metabolism, enters the Krebs cycle in skeletal muscles and the renal cortex.

- In severe liver failure and severely reduced muscle perfusion, metabolic clearance of citrate is diminished.

- Insufficient citrate metabolism/citrate accumulation results in decreasing levels of ionized calcium in the patients' blood.

- To compensate for this, the calcium compensation must be increased, for example from 100%→110%→120%→130% and so on.

- This is the first sign of insufficient calcium metabolism/citrate accumulation.

- Stable ionized calcium levels strongly indicate that the citrate metabolism is sufficient.

- If calcium compensation continuously must be increased, that indicates that citrate accumulation is at hand and the total to ionized calcium ratio should then be checked. A ratio ≥2.4 indicates accumulation and an increased mortality rate (19).

- In critically ill patients with liver cirrhosis, citrate clearance is up to 54 % lower than clearance in non-cirrhotic critically ill patients (20).

- If citrate anticoagulation is applied in patients with liver cirrhosis, more frequent monitoring of citrate accumulation is advised.

- Clinical experience has shown that patients with compensated liver cirrhosis tolerate anticoagulation with citrate.

- Patients with septic shock and lactic acidosis, in whom a limited metabolism of citrate might be expected due to disturbed liver and muscle perfusion, can generally be anticoagulated with citrate without signs of accumulation (20).

- If accumulation occurs, the citrate dose/load should be reduced to a level that allows a stable calcium compensation level and a total to ionized calcium ratio of <2.25.

- If this cannot be achieved, citrate anticoagulation should be stopped.

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