

Citrate anticoagulation during CRRT for acute kidney injury

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Summary

This article discusses the use of citrate anticoagulation during continuous renal replacement therapies (CRRTs) which are prescribed for patients with severe acute kidney injury (AKI). Where heparin was traditionally the anticoagulant of choice for CRRT, regional citrate anticoagulation (RCA) has now emerged as the safest and most effective way of anticoagulating blood during CRRT.

Continuous renal replacement therapy (CRRT), which involves extracorporeal filtration/dialysis of patient blood, is a mainstay treatment option for those with severe acute kidney injury (AKI). Anticoagulation of the extracorporeal circuit is essential to the efficacy of this treatment.

Traditionally, heparin has been the anti-coagulant of choice for CRRT, but in recent years citrate has emerged as the preferred anticoagulant. Although citrate anticoagulation has safety advantages over heparin anticoagulation, it is associated with risk of acid-base and electrolyte disturbances that are a focus of this article. The link between citrate anticoagulation and these biochemical disturbances will be explained, and the necessity for close biochemical monitoring of patients receiving citrate-anticoagulated CRRT high-lighted.

The article begins with a very brief overview of AKI and a general consideration of renal replacement therapies (RRT) that will place CRRT in its wider context.

Acute kidney Injury

Acute kidney injury (AKI), a clinical syndrome with many possible causes, is simply defined as an abrupt decrease in kidney function over a period of hours or days, evidenced by recent increase in serum creatinine concentration and/or reduction in urine output [1].

It is distinct from chronic kidney disease (CKD) in which decrease in kidney function is slowly but irreversibly progressive, occurring over a period of months and years. AKI can of course occur in those with underlying CKD, and a diagnosis of AKI is associated with greater than normal risk of an eventual diagnosis of CKD [2].

Internationally agreed guidelines [1] state that a diagnosis of AKI can be made if:

- serum creatinine increases by ≥ 0.3 mg/dL (26.5 $\mu\text{mol/L}$) within 48 hours; or
- there has been a 50 % or greater increase in serum creatinine within the past 7 days; or
- urine volume is < 0.5 mL/kg/h for 6 hours

Stage	Serum Creatinine	Urine output
1	1.5-1.9 times baseline OR ≥ 0.3 mg/dL (26.5 $\mu\text{mol/L}$) increase	< 0.5 mL/kg/h for 6-12 hours
2	2.0-2.9 times baseline	< 0.5 mL/kg/h for ≥ 12 hours
3	3.0 times baseline OR Increase in serum creatinine to ≥ 4.0 mg/dL (353.6 $\mu\text{mol/L}$) OR Initiation of renal replacement therapy	< 0.3 mL/kg/h for ≥ 24 hours OR Anuria for ≥ 12 hours

TABLE I: The three stages of AKI severity (from ref 1)

AKI encompasses the full spectrum of severity from a mild decrease in kidney function (stage 1 AKI) to renal failure (stage 3 AKI). Staging depends on serum creatinine measurement, with or without urine output data (Table I).

The causes of AKI are conventionally classified under three headings: prerenal; renal (intrinsic); and postrenal, emphasizing the fact that AKI can have a specific renal etiology but can also result from primary problem outside the kidney.

Any condition that has the effect of reducing blood flow to the kidney (renal perfusion) is a potential cause of prerenal AKI; these conditions include: hypovolemia due to vomiting, diarrhea, hemorrhage, burns or septic shock; and reduced cardiac output due to, for example, heart failure and liver failure (cirrhosis). The major cause of intrinsic AKI is renal tubular necrosis, resulting from renal ischemia or ingestion of nephrotoxic drugs/toxins.

Sepsis, the most common cause of AKI in the critically ill, is due in part to poorly defined intrinsic renal injury akin to renal tubular necrosis [3]. Finally, postrenal AKI results from any condition that obstructs urine flow distal to the kidney; these include: renal stones (calculi); prostate disease (tumor/hypertrophy); bladder dysfunction; and urethral stricture.

Given the range and frequency of clinical conditions that can give rise to AKI, it is to be expected that AKI can occur in both community and hospitalized patients; but the group most frequently and severely affected is critically ill patients admitted to intensive care.

A recent study of 1802 patients in 97 ICUs across 33 countries [4] found that using the KDIGO definition for AKI diagnosis and staging described above AKI is present in 57 % of ICU patients (18.4 %, stage 1 AKI; 8.9 %, stage 2 AKI; and 30 %, stage 3 AKI). Two AKI etiologies, sepsis and hypovolemia, together

accounted for the majority (74.8 %) of AKI cases in this study cohort.

Management of AKI – renal replacement therapies for AKI

There is no specific treatment for AKI and management is largely supportive with treatment directed at the underlying cause. Withdrawal of nephrotoxic drugs, fluid resuscitation, and correction of electrolyte and acid-base disturbance are all part of this general supportive management [5]. Administration of vasopressor or inotropic drugs to restore normal blood pressure and cardiac output may be necessary.

Renal replacement therapy (RRT), the focus of this article, represents the last-resort treatment for patients with severe AKI that does not respond to conservative supportive management. Around 23 % of ICU patients with AKI (i.e. around 13 % of all ICU patients) receive RRT [4].

Renal replacement therapy (RRT) is the generic term for all treatments seeking to replace kidney function. Transplantation of donor kidney to those with end-stage renal disease can be considered the ultimate RRT [6], but the term is more often reserved for those therapies that replace the blood filtering and homeostatic functions of the kidney by dialysis, a process that utilizes a semi-permeable membrane as the blood filter. Two broad types of dialytic RRT are available for treatment of AKI (and for that matter, end-stage CKD): peritoneal dialysis and hemodialysis.

Peritoneal dialysis (PD) [7] allows blood filtering to occur within the body; the technique takes advantage of the filtering properties of the peritoneum, a “natural” semi-permeable membrane. The treatment involves administration of dialysis fluid (dialysate) to the peritoneal cavity and draining of the fluid from the body. This drained fluid contains waste products and excess water that have passed from blood across the peritoneal membrane.

By contrast, hemodialysis involves filtering blood in a machine outside the body (extracorporeal). Blood is pumped to the filter/dialyzer, where waste products and excess fluid are removed, and then returned to the body. This extracorporeal circuit (the dialysis machine and its connecting tubes from and back to the patient) is a procoagulant environment.

Hemodialysis, hemofiltration and hemodiafiltration

Modern dialysis machines have the option for hemofiltration (HF) as well as hemodialysis (HD), allowing the possibility of three different dialytic modalities for the treatment of AKI: hemodialysis (HD); hemofiltration (HF); and hemodiafiltration (HDF).

At the core of all three modalities is the semi-permeable membrane that constitutes a blood filter. As blood pumped from the patient flows on one side of this membrane, excess water and waste solutes pass across the membrane. The filtrate or effluent is pumped to waste as the filtered blood is returned to the patient.

The process of hemodialysis (HD) [8, 9] involves the use of a dialysis fluid that flows continuously and countercurrently to blood on the other side of the membrane. The composition and flow rate of dialysis fluid ensures a constant concentration gradient across the semi-permeable membrane with respect to blood solutes. These concentration gradients in turn facilitate controlled diffusion of solute molecules across the membrane.

For solutes like urea and creatinine, which must be removed from blood, the concentration gradient is such that the direction of diffusion is from blood to dialysis fluid, whereas for solutes like bicarbonate, which must often be added to blood to correct the acidosis associated with severe AKI, dialysis fluid with high bicarbonate concentration relative to blood ensures that diffusion is in the opposite

direction, from dialysis fluid to blood. Adjustment of dialysis fluid composition and flow rate thus allows patient-specific metabolic correction.

Fluid excess is often a feature of AKI that is corrected during hemodialysis. This is achieved by ultrafiltration, which depends on the hydrostatic pressure gradient that exists across the semi-permeable membrane. The relative positive hydrostatic pressure on the blood side of the membrane effectively "pushes" water from blood to dialysis fluid.

This ultrafiltration also facilitates passage of solute molecules, which are dragged along with water during ultrafiltration by a mechanism called solute convection (or solvent drag). The combined effect of solute diffusion, solute convection and ultrafiltration during hemodialysis aims to ensure that fluid volume and composition within both extracellular and intracellular compartment is restored, as close as is possible, to that which pertains among those with normally functioning kidneys.

Hemofiltration (HF) [9] differs from HD in that no dialysis fluid is used, so that solute diffusion does not occur. Ultrafiltration and associated solute convection is the only mechanism operating in HF. A large amount of fluid (2-3 liters/hour) is removed during HF and this requires replacement with a sterile fluid that resembles blood plasma in composition. This replacement fluid is continuously added to blood as it enters the filter (predilution) or as it leaves the filter (postdilution).

Hemodiafiltration (HDF) is the combination of HF and HD. It allows optimal clearance of low-molecular-weight solutes by diffusion to dialysis fluid, combined with optimal clearance of high-molecular-weight solutes by convection and ultrafiltration. As with HF, HDF requires continuous replacement fluid; and as with HD, HDF requires dialysis fluid.

Initiation and timing of RRT for AKI – intermittent versus continuous RRT

All renal replacement therapies (PD, HD, HF and HDF) can be delivered intermittently (i.e. typically in 3-4 hourly sessions) or continuously until kidney function is restored. For patients with end-stage renal failure, who require life-long (chronic) RRT, the treatment is exclusively intermittent hemodialysis (IHD), almost invariably delivered in four hourly sessions, three times a week [8].

Patients with AKI only have a temporary requirement for RRT to support renal function during resolution of the critical/acute illness that precipitated AKI. The mean duration of RRT among patients with AKI is around 13 days [10], although in particular cases it may only be necessary for a few days, or extend for many weeks.

Traditional (absolute) indicators for initiation of RRT in AKI include:

- hyperkalemia (plasma potassium > 6.0-6.5 mmol/L)
- severe uremia (plasma urea > 30 mmol/L)
- signs of uremic encephalopathy
- acidosis (pH < 7.25, bicarbonate < 10 mmol/L)
- acute pulmonary edema

It may be beneficial to start treatment before these extreme effects of AKI are evident, but optimal timing for initiating (and stopping) RRT is currently unclear [1] and the subject of ongoing research [11, 12]. There is currently no reliable data to support a particular type of RRT for AKI and consequently all types of RRT have been employed.

Current guidelines [1], however, reflect a consensus that, whatever the modality, RRT should be delivered continuously rather than intermittently to the most critically ill (hemodynamically unstable) patients. Recent surveys [13, 14] indicate that nowadays continuous renal replacement therapies (CRRTs) are used much more frequently than

intermittent therapies for AKI, and that the most commonly used CRRT is continuous venous venous hemofiltration (CVVHF), followed by continuous venous venous hemodiafiltration (CVVHDF).

Anticoagulation during continuous renal replacement therapy (CRRT)

CRRT, in common with all other renal replacement therapies except peritoneal dialysis, involves pumping blood through a non-physiological, extracorporeal circuit. The inherent property of blood to coagulate (clot) on contact with non-physiological surfaces determines that in order to maintain a "clot-free" patient extracorporeal circuit, blood must be anticoagulated.

CRRT has a particular need for anticoagulation, compared with intermittent modalities, because of the prolonged treatment sessions, and the relatively slow rate at which blood is pumped through the circuit [15]. Additionally, the blood of patients who require CRRT is often already in a relative procoagulant state due to underlying critical illness (e.g. sepsis) or trauma [16].

For many years heparin, either unfractionated heparin (UF) or low-molecular-weight heparin (LMWH), was the only anticoagulant used in dialytic procedures, including CRRT. Heparin continues to be used; it is a cheap and generally safe means of anticoagulation for the majority of patients requiring RRT.

However, systemic heparin anticoagulation, which cannot be avoided, inevitably carries with it an increased risk of bleeding, so that heparin anticoagulation during dialytic procedures is absolutely contraindicated for those who are currently bleeding or at higher than normal risk of bleeding.

Additionally, heparin can, in a small minority (<5%) of patients, cause an immune-mediated condition called heparin-induced thrombocytopenia (HIT)

type II that is associated with massive reduction in platelet numbers and the risk of life-threatening thrombosis [17].

The potential bleeding and HIT-II risks associated with heparin use highlighted the need for an alternative anticoagulant for some patients requiring RRT. Citrate provided such an alternative.

Regional citrate anticoagulation of the dialysis circuit, first used successfully in the early 1980s [18], was originally reserved for that small minority of patients for whom heparin is contraindicated. That changed with results of randomized controlled trials comparing heparin-anticoagulated CRRT with citrate-anticoagulated CRRT; these demonstrated that citrate is both a more effective and safer anticoagulant than heparin [19, 20].

Citrate has consequently emerged in recent years as the anticoagulant of choice for all AKI patients requiring CRRT [1, 15]. Intensive care units around the world are now reporting switching from heparin to regional citrate anticoagulation for CRRT [21]. Some authorities [22] are even recommending the use of citrate rather than heparin anticoagulation for intermittent (chronic) hemodialysis (IHD).

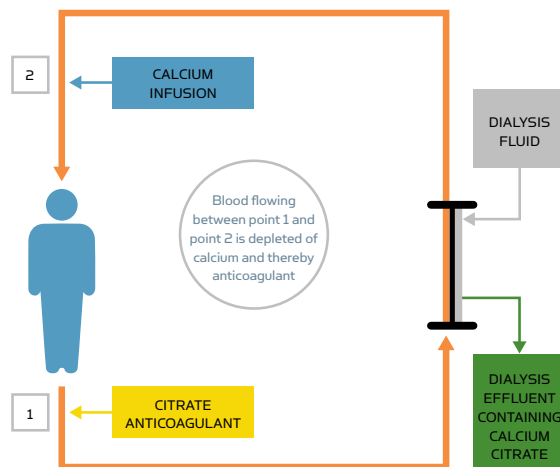
Citrate – the mechanism of its anticoagulant action and its application in CRRT

Citrate, which has been used to anticoagulate/preserve donated blood for transfusion for well over a century [23], prevents blood from clotting through its capacity to bind (chelate) the ionized calcium (iCa) that circulates in blood plasma. This iCa is a necessary cofactor for both platelet aggregation and several key steps in the intrinsic and extrinsic coagulation pathways that are responsible for fibrin production, and thereby, fibrin clot formation.

Blood coagulation is prevented by reduction in plasma iCa concentration to around 0.35 mmol/L (normal ref range 1.15-1.30 mmol/L). This non-

physiological, severely hypocalcemic state is achieved by raising plasma citrate concentration to around 3 mmol/L [24] (normal plasma citrate concentration ~0.1 mmol/L [25]).

Although there are differences in detail outlined by Morabito *et al* [24], all protocols for citrate anticoagulation during CRRT involve the continuous infusion of citrate-containing solution (usually either trisodium citrate or acid-citrate-dextrose (ACD) solution) to the prefilter/dialysis line, close to where it leaves the patient, either as a separate solution or combined with predilution replacement fluid. The flow rate of this infusion is adjusted to achieve a blood citrate concentration of ~3 mmol/L, and thereby a plasma iCa of around 0.35 mmol/L.



The hypocalcemia induced by citrate infusion is corrected before blood returns to the patient, by infusion of calcium-containing solution (calcium chloride or calcium gluconate) to the postfilter line close to where it enters the patient (see the figure above).

The major safety advantage of citrate anticoagulation over heparin anticoagulation is that anticoagulation is confined to the extracorporeal circuit. This so-called "regional anticoagulation" is achieved because most of the infused citrate is removed (as either citrate anions or calcium-citrate chelate) from blood during passage through the filter/dialyzer [24].

Any remaining citrate in postfilter blood is diluted in systemic circulation and rapidly metabolized to carbon dioxide and water by the oxygen-dependant Krebs cycle in the mitochondrion of tissue cells (predominantly liver cells [24]).

Metabolism of citrate is associated with production of bicarbonate: for each 1 mmol citrate metabolized, 3 mmol bicarbonate is generated. The rapid clearance of citrate (half-life of citrate in blood is normally around 5 minutes [26]) via this principally hepatic route normally ensures the absence of systemic anticoagulation during CRRT, and thereby no additional risk of bleeding.

Potential metabolic disturbances during citrate-anticoagulated CRRT

The apparent reluctance to fully embrace citrate-anticoagulated CRRT for all AKI patients until recently has been attributed to concern regarding the acid-base and electrolyte disturbances that may occur in patients receiving the treatment [15, 24].

The following electrolyte and acid-base disturbances have been reported in patients receiving citrate-anticoagulated CRRT [24]:

- hypocalcemia/hypercalcemia
- hypomagnesia/hpermagnesia
- hyponatremia/hypernatremia
- metabolic alkalosis
- metabolic acidosis

These disturbances can arise for a number of reasons but accumulation of citrate in the peripheral circulation (citrate toxicity) can be central to most of these disturbances. Reasons why citrate may accumulate during CRRT include:

- Impaired metabolism of citrate due to liver disease and/or reduced delivery of oxygen because of inadequate perfusion (e.g. in septic/cardiogenic shock)

- Progressive reduction in membrane patency during dialysis with consequent reduced filtration of citrate and concomitant increase in citrate delivery to systemic circulation
- Operational error – accidental increased rate of citrate infusion to the extracorporeal circuit and concomitant increased delivery of citrate to systemic circulation
- Blood product transfusion – citrate preservative present in blood products adds to the citrate load in systemic circulation arising from CRRT

Irrespective of the cause, accumulation of citrate in the peripheral circulation can result in citrate chelation of circulating ionized calcium, with consequent reduced plasma ionized calcium concentration (hypocalcemia). If sufficiently severe hypocalcemia can cause cardiac arrhythmia and, ultimately, cardiac arrest [27].

Although plasma ionized calcium is reduced during citrate accumulation (toxicity), total calcium is increased (indicating hypercalcemia) because the calcium bound to citrate is included in measured total calcium. An increase in the ratio of total to ionized calcium (normally 2.0) to > 2.1 has been found to be the most reliable signal of citrate toxicity in the absence of routinely available plasma citrate estimation [24].

Hypo- and hypercalcemia can also occur, independently of any effect of citrate in the peripheral circulation, if postfilter calcium infusion rate is not well matched to the calcium loss during blood flow through the filter. In this instance there is no effect on calcium ratio; both total and ionized calcium are reduced (or increased) to the same degree.

Delivery of a high citrate load to a patient who has the capacity to metabolize it can cause excessive bicarbonate production, consequent on increased citrate metabolism, with resulting metabolic alkalosis. Of all biochemical disturbances associated with citrate anticoagulation, metabolic

alkalosis is probably the most common, occurring in 50 % of patients in one study [28].

Inadequate citrate metabolism and consequent accumulation of citric acid that can occur in those with advanced liver disease and/or inadequate tissue perfusion is the cause of the metabolic acidosis that can occur in patients receiving citrate anticoagulation [24]. Preexisting lactic acidosis in these patients may be a contributory factor to development of metabolic acidosis.

The risk of increased plasma sodium (hyponatremia) associated with citrate anticoagulation is due to the high sodium content (hypertonicity) of some citrate solutions used in CRRT. For example, the 4 % solution of trisodium citrate that is used in some protocols contains sodium at a concentration of 420 mmol/L. In practice, the use of hypotonic dialysis/replacement fluids can mitigate this risk and hyponatremia is by all accounts a rare complication of citrate anticoagulation [24].

The risk of hypomagnesemia (reduced serum magnesium) during citrate anticoagulation reflects the fact that, in common with calcium, magnesium is a divalent ion that can also bind to (chelate) citrate. If magnesium losses due to the chelation action of citrate are not fully compensated for by magnesium in dialysis/replacement fluids, hypomagnesemia can occur [29].

Biochemical monitoring of patients receiving citrate-anticoagulated CRRT

Given the potential for biochemical disturbance during citrate-anticoagulated CRRT, safe and effective delivery depends on identifying these disturbances rapidly and responding with adjustment to the dialysis prescription in an appropriate and timely way. The table below summarizes the necessary biochemical testing.

Point-of-care testing using a blood gas analyzer

sited within the intensive care unit allows rapid and convenient measurement of most parameters (ionized calcium, pH, bicarbonate, base excess, sodium and lactate) but serum total calcium and magnesium estimation are not usually available on these platforms and samples must be sent to the laboratory for these measurements.

Two recent studies [30, 31] provide evidence that some blood gas analyzers may not be reliable in measuring ionized calcium at the extremely low, non-physiological concentrations (~0.3 mmol/L) present in postfilter blood, although their ability to accurately measure plasma ionized calcium in systemic circulation (where the concentration is much higher) is not in doubt.

Before using a blood gas analyzer to monitor patients receiving citrate-anticoagulated CRRT it is advisable to consult with the vendor of the blood gas machine and confirm that the instrument has been well validated to measure ionized calcium at the very low concentration (in the range of 0.15-0.4 mmol/L) that may prevail in postfilter samples.

Summary

Continuous renal replacement therapies (CRRTs) are prescribed for patients with severe acute kidney injury (AKI). They involve pumping blood through an extracorporeal circuit. In order to prevent blood from clotting within this non-physiological environment it is necessary to artificially anticoagulate blood.

In recent years regional citrate anticoagulation (RCA) has emerged as the safest and most effective way of anticoagulating blood during CRRT. RCA is associated with risk of electrolyte and acid-base disturbances, including life-threatening hypocalcemia. Regular biochemical monitoring as out-lined in the table below is therefore mandatory for patients receiving RCA-anticoagulated CRRT.

Parameter measured	Monitoring interval	Target values or approx. reference ranges	Purpose of measurement	Corrective action if outside target
Postfilter ionized calcium (iCa) concentration, i.e. blood sampled from postfilter port	Within 1 hour of start and after any citrate dose change, then every 4-6 hours	0.25-0.35 mmol/L	<ul style="list-style-type: none"> To confirm that blood within the extracorporeal circuit is fully anticoagulated Necessary to ensure maximal filter life and effective dialysis 	Adjustment of citrate dose: increase if iCa > 0.35, decrease if iCa < 0.25
Systemic ionized calcium (iCa), i.e. blood sampled from patient	Baseline (before starting), then 1 hour after starting, then at least every 4-6 hours	1.15-1.30 mmol/L	<ul style="list-style-type: none"> Baseline measurement used to set initial calcium infusion rate Subsequent measurements used to detect systemic hypocalcemia/hypercalcemia Allows determination of TotCa:iCa ratio (see below) 	Adjustment of calcium infusion rate; increase if iCa < 1.15; decrease if iCa > 1.30
Systemic total calcium (TotCa), i.e. blood sampled from patient (TotCa = iCa + calcium bound to albumin + calcium bound to citrate)	At least every 12-24 hours (must be simultaneous to systemic ionized calcium estimation)		Only required for determination of TotCa:iCa ratio (see below)	

Ratio of total to ionized calcium (TotCa:iCa)	At least every 12-24 hours	< 2.1	To detect citrate accumulation/toxicity – sometimes called “citrate lock”	Options include: <ul style="list-style-type: none"> • Reduced rate of citrate delivery • Temporarily halt citrate infusion • Abandon citrate anticoagulation in favor of heparin
Arterial blood gas analysis <ul style="list-style-type: none"> • pH • bicarbonate • base excess (BE) 	Baseline (before starting) . Within 1 hour of starting, then at least every 4-6 hours.	pH 7.35-7.45 bicarb 23-28 mmol/L BE -2-+3 mmol/L	To detect acid-base disturbances: metabolic alkalosis metabolic acidosis	Options in the case of metabolic alkalosis include: <ul style="list-style-type: none"> • Decrease citrate • Increase bicarbonate losses to effluent • Reduce bicarbonate in dialysate/ replacement fluid
Serum sodium	Once daily	135-145 mmol/L	To detect hypernatremia/hyponatremia	Rare occurrence – verify correct dialysis/ replacement fluid
Serum lactate	Baseline (before starting), then according to clinical needs	< 2.0 mmol/L	To help identify those who are at risk of citrate toxicity	Consider, along with TotCac: iCa ratio, risk of citrate toxicity
Serum magnesium	At least once daily		To detect hypomagnesia	Correction with magnesium infusion

TABLE II: Biochemical monitoring during citrate-anticoagulated CRRT (Ref 24)

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