Use of tri-sodium citrate in hemodialysis

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Hemodialysis and related treatments for those with failing kidneys all involve blood flow through a circuit outside the body. This extracorporeal circuit - the dialysis machine and its connections from and back to the body - is a non-physiological, pro-coagulant environment.

To counter the tendency for patients’ blood to clot during flow through this extracorporeal circuit, anticoagulant agents that temporarily inhibit the normal clotting process are employed. Historically, heparin was the only anticoagulant used for this purpose, and whilst it remains the standard mode of anticoagulation, there are alternatives that may be better suited in some circumstances.

Tri-sodium citrate, the focus of this article, is one such alternative. The article will include consideration of the anticoagulant properties of citrate, some detail of how tri-sodium citrate is used to anticoagulate the dialysis pathway, and the advantages of using citrate rather than standard heparin anticoagulation.

The use of tri-sodium citrate is not without risk; the potentially harmful metabolic changes, including disturbance of acid-base balance, that can be associated with tri-sodium citrate anticoagulation will be discussed. The article begins with a very brief outline of the range of hemodialysis modalities used to treat those with failing kidneys.

Renal replacement therapy

Renal replacement therapy (RRT) is the generic term for all treatments seeking to replace the excretory function of the kidneys. RRT includes hemodialysis (HD) and two related treatments, hemofiltration (HF) and hemodiafiltration (HDF) - all a focus of this article - along with peritoneal dialysis and kidney transplantation, which need not be considered further here.

In the UK, which is broadly representative of other developed countries, close to 50,000 patients (747 per million population) with end-stage chronic kidney
disease (CKD), most commonly the result of long-standing diabetes, are currently receiving RRT, and each year around 6500 (108 per million population) are added to the list [1].

Of these, around two thirds receive regular, planned hemodialysis, usually of 4 hours duration, three times a week. For some patients this conventional intermittent hemodialysis (IHD) schedule aims to preserve life until kidney transplantation. Those end-stage CKD patients not scheduled for transplantation must continue with the IHD treatment for life.

The other main group that might require RRT is critically ill patients with acute kidney injury (AKI, formerly called acute renal failure) [2]. This is defined as abrupt or rapid decline of renal function and is most often due not to primary disease of the kidney but some catastrophic acute illness such as systemic infection or severe trauma that results in circulatory collapse and multiple organ failure [3].

Unlike CKD, which progresses irreversibly but slowly over a period of years or decades to end-stage CKD and the need for RRT, AKI develops rapidly over a period of hours or days, but is potentially reversible. For patients with AKI, RRT in the form of hemodialysis, hemofiltration or hemodiafiltration provides life-preserving short-term renal support as part of the overall treatment for the critical illness/trauma that induced the kidney injury.

Normal kidney function usually returns with successful treatment of the underlying critical illness/trauma. Approximately 4-5 % of intensive care patients have AKI of sufficient severity to warrant RRT, and the number of critically ill patients receiving RRT has doubled in the past 20 years [4]. This is due in part to the recognition that starting RRT early improves the chances of surviving critical illness associated with loss of renal function.

Hemodialysis (HD), hemofiltration (HF) and hemodiafiltration (HDF)

All of these renal replacement therapies (RRTs) involve blood flow through a machine outside the body. At the core of all three types of therapy is the semi-permeable membrane (or dialyzer membrane) that constitutes a blood filter.

As blood pumped from the patient passes on one side of this semi-permeable membrane, excess water and solutes pass from blood across the membrane. This physiologically unwanted water and solutes (the filtrate or effluent) is directed to waste, and the filtered blood is returned to the patient.

The process of hemodialysis (HD) [5] involves the use of a dialysate fluid that flows continuously and countercurrently to blood on the other side of the semi-permeable membrane.

The composition and flow of dialysate fluid ensures a constant concentration gradient across the semi-permeable membrane for the solutes in blood. These concentration gradients in turn facilitate controlled diffusion of solutes across the membrane.

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

Adjustment of dialysate fluid composition thus allows patient-specific metabolic correction.

Fluid excess is an invariable feature of renal failure that is corrected during hemodialysis. The movement of water from blood to the dialysate side of the membrane is achieved by a hydrostatic pressure gradient across the membrane.

The relative negative pressure on the dialysate side of the membrane effectively sucks water from blood to dialysate - a process called ultrafiltration. Passage of large solute molecules from blood across the semi-permeable membrane depends not on diffusion down
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Intermittent versus continuous RRT

The three RRT modalities discussed above can be delivered intermittently or continuously. Those with end-stage CKD, who are otherwise healthy, receive exclusively intermittent hemodialysis (IHD); that is, typically, sessions of 4-hour duration, three times a week [5]. This allows a near-normal lifestyle between scheduled treatments.

For critically ill patients with AKI, continuous RRT (HD, HF or HDF), rather than conventional intermittent RRT has, over the past decade or two, become an increasingly prescribed treatment [3, 6].

This is principally because critically ill patients are typically hemodynamically unstable and consequently less tolerant of the extreme fluxes of blood volume and solute (e.g. electrolyte) concentration necessarily induced by episodic RRT of a few hours duration [6].

In contrast with intermittent RRT, continuous RRT allows much more gentle flux in solute concentration and fluid volume that more closely mimics the physiological fluxes associated with the subtle minute by minute adjustments made by normally functioning kidneys. Sudden, life-threatening decline in blood pressure (hypotension) is just one of several significant risks for critically ill patients exposed to intermittent RRT that are ameliorated by the use of continuous RRT [3, 6].

Despite the potential advantages for the critically ill patient, continuous RRT poses logistical problems associated with having critically ill patients continuously attached to a dialysis machine, rather than for just a few hours each day.

A recent review [6] addresses the many issues surrounding the choice of continuous versus intermittent RRT for the critically ill. The choice has important implication for anticoagulation of the extracorporeal circuit.

Anticoagulation of the extracorporeal circuit - some general considerations

The inherent property of blood to coagulate (clot) on contact with non-physiological surfaces was a major obstacle for those involved in the early development of hemodialysis treatments [7].

A number of factors contribute to the tendency for blood to clot within the dialysis circuit [8-10]. Both the intrinsic and extrinsic coagulation pathways that together generate the fibrin necessary for blood clot (thrombus) formation are activated during blood flow...
through the dialysis machine. Contact activation of intrinsic pathway is initiated by deposition of plasma proteins on the dialysis membrane (and other non-physiological surfaces within the circuit) [11].

The extrinsic pathway is activated by tissue factor protein released from activated white blood cells (granulocytes and monocytes) following adherence of these cells to the dialysis membrane. Additionally, the shear stress associated with blood flow through this non-physiological environment causes platelet activation and aggregation, both necessary events for thrombus formation.

Slow blood flow (relative stasis) at particular points along the extracorporeal circuit, and for short periods during treatment sessions, greatly potentiate thrombus formation, as does contact of blood with air (in bubble traps within the extracorporeal circuit). Quite apart from the thrombogenicity of the dialysis process, some patients (e.g. those with sepsis, those with raised hematocrit) may already be in a pro-coagulant state prior to dialysis.

Coagulation within the extracorporeal circuit is associated with accumulation of cells, proteins and microthrombi on the membrane (filter) and progressive deterioration of membrane patency with resulting reduced effectiveness of dialysis, and ultimately, if the filter is not renewed, thrombosis of the dialysis circuit.

The standard strategy to minimize blood clotting within the dialysis circuit is to anticoagulate (artificially reduce the coagulability of blood) with unfractionated (UF) heparin [2, 9, 10].

Anticoagulation with heparin

The anticoagulant property of heparin, which has well-established therapeutic value beyond RRT [12], is due to its capacity to bind anti-thrombin III. This is one of a number of anticoagulant proteins normally present in blood plasma, whose collective function is modulation of the clotting process by inhibition of clotting factors of the intrinsic and extrinsic coagulation pathway.

The anticoagulant effect of anti-thrombin III, which operates specifically by inhibition of thrombin and factors Xa, VII, IXa, is increased by a magnitude of several thousand when it is bound to heparin. For extracorporeal RRTs, unfractionated heparin is administered into the prefilter line that conveys blood from the patient to the dialyzer/filter, usually as a single loading dose of 500-1000 IU followed by a continuous infusion (500-1000 IU/hour). The infusion is stopped at least 1 hour before the end of treatment session [10].

Whilst use of heparin in this way significantly reduces blood clot formation within the dialysis pathway, it inevitably results in systemic anticoagulation. Consequently, for the duration of dialysis/filtration, and until heparin is cleared from the body, patients are at greater than normal risk of bleeding. (The half-life of unfractionated heparin in plasma is normally 90 minutes but can be up to 3 hours in those with renal insufficiency [8].)

Monitoring of heparin dose effect is thus prudent to avoid both underheparinization (with resulting clot formation within the extracorporeal circuit) and overheparinization (with resulting occult or overt blood loss from the patient).

The whole-blood activated partial thromboplastin time (APPT) test and activated blood clotting time (ACT) test are both effective for monitoring the effect of unfractionated heparin and available as point-of-care tests. During hemodialysis, optimum ACT is 80 % above baseline (predialysis) level [9]. For those patients at greater than normal risk of bleeding, a lower dose of heparin is indicated and for these patients the ACT target is just 40 % above baseline level [9].

Such a low target inevitably increases the risk of blood clots forming within the dialysis circuit.

Clearly, with intermittent dialysis the systemic anticoagulation that necessarily results from the use of heparin only persists for not much longer than the duration of the treatment session (4-5 hours).
By contrast patients receiving continuous dialysis anticoagulated by heparin are systemically overcoagulated for extended periods (days or maybe weeks). The attendant risk of bleeding that results from heparin anticoagulation is thus greater for those receiving continuous RRT, compared to those receiving intermittent RRT. This greater theoretical risk was one of the principal obstacles that delayed adoption of continuous RRT for the critically ill [6].

Although unfractionated heparin provides a cheap, reliable and generally safe means of anticoagulation for the vast majority of patients requiring RRT, there are two groups of patient for whom heparin anticoagulation is absolutely contra-indicated.

The two groups are: those who are currently bleeding or at particularly high risk of bleeding due to, for example, an inherited or acquired coagulopathy or recent surgery; and those with a condition called heparin-induced thrombocytopenia (HIT) - type II. HIT-II is a life-threatening adverse effect of heparin therapy that occurs in up to 5 % of patients given unfractionated heparin.

It is caused by production of an antibody directed at an antigenic component of the heparin-platelet 4 complex present in the plasma of patients given heparin. Antibody binding of the complex results in thrombogenic platelet activation and a greater than 50 % reduction in the number of circulating platelets (severe thrombocytopenia) within a few days of heparin administration [10, 12].

These patients must avoid all forms of heparin (both unfractionated and low-molecular-weight heparin (LMWH) preparations).

Tri-sodium citrate provides one of several alternative means of anticoagulation during RRT [9, 10] for patients who for one reason or another cannot safely tolerate standard heparin anticoagulation.

The anticoagulant action of tri-sodium citrate

Tri-sodium citrate owes its anticoagulant property to the capacity of citrate to bind (chelate) the ionized calcium circulating in blood plasma. This ionized calcium is a necessary co-factor for both platelet aggregation and plasma fibrin production by intrinsic and extrinsic coagulation pathways [12].

Blood coagulation is prevented by reduction of plasma ionized calcium concentration to < 0.33 mmol/L [13] (normal plasma ionized calcium concentration 1.15-1.30 mmol/L). This hypocalcemic state can be achieved by raising plasma citrate concentration to around 4-5 mmol/L [14] (normal plasma citrate concentration ~ 0.1 mmol/L [15]).

Although there are differences in detail, all protocols for tri-sodium citrate anticoagulation during RRT involve continuous infusion of a tri-sodium citrate solution to the prefilter line - either as a separate solution or combined with predilution replacement fluid - the object being to maintain the prefilter blood citrate concentration at a level (~ 4-5 mmol/L) that ensures plasma ionized calcium concentration of blood flowing through the extracorporeal circuit is reduced to < 0.35 mmol/L.

The major advantage of citrate anticoagulation over conventional heparin anticoagulation is that it does not result in systemic anticoagulation. Blood is only anticoagulated for the duration of its passage through the extracorporeal circuit.

This so-called “regional anticoagulation” is achieved because most (50-60 %) of the tri-sodium citrate-calcium chelate diffuses across the membrane and is thereby removed from blood [14]. Any remaining tri-sodium citrate present in blood passing from the filter is diluted in the systemic circulation and converted to citric acid by reaction with carbonic acid (with generation of bicarbonate).

Citric acid is then rapidly metabolized to carbon dioxide and water by the Krebs cycle in the mitochondria of
tissue cells (predominantly liver and skeletal muscle cells [16]). Half-life of citrate in plasma is just 5 minutes [17], far shorter than that of heparin.

The hypocalcemia, induced by citrate infusion that ensures anticoagulation within the extracorporeal circuit, is corrected postfilter by continuous infusion of a calcium-containing solution (calcium chloride or calcium gluconate).

Theoretically, so long as tri-sodium citrate is infused at a point close to where blood exits from the patient, and replacement calcium infused at a point close to where blood re-enters the patient (or via a separate venous line directly to systemic circulation), the whole of the extracorporeal circuit is well anticoagulated, but there is no systemic hypocalcemia or hypercitratemia, and therefore no systemic anticoagulation.

The patient thus remains at no greater risk of bleeding as a result of exposure to the dialysis treatment.

Validation of tri-sodium citrate anticoagulation

The first attempt to exploit tri-sodium citrate as an anticoagulant for dialysis was by Morita and colleagues at Wayne State University in Detroit in 1961 [18]. Although this demonstrated proof of principle and the potential for associated metabolic derangement (to be discussed later), no further progress was made over the following 2 decades.

Current protocols for tri-sodium citrate anticoagulation have their origins in the first successful trial conducted in Kansas in the early 1980s [19]. For this trial, four critically ill patients with acute renal failure complicated by active bleeding received IHD anticoagulated with tri-sodium citrate.

A total of 15 dialysis sessions of 4 hours duration were delivered to these four patients. (At this time continuous RRT was yet to be introduced to critical care.) Additionally, the same novel citrate anticoagulation protocol was used on six occasions for the dialysis of four CKD patients receiving regular long-term IHD.

For the anticoagulation protocol, an iso-osmotic solution of tri-sodium citrate (102 mM) was infused at a rate of 5-10 mL/minute into the line directing blood from the patient. With an arbitrarily set blood flow rate of 200 mL/minute, this rate of infusion ensured a final blood citrate concentration of 2.5-5.0 mM within the dialysis circuit.

Previous in vitro experiments for this trial had demonstrated that this would extend whole-blood clotting time (within the circuit) of all patients to > 20 minutes. Blood was dialyzed against a specially prepared calcium-free dialysis fluid flowing at a rate of 500 mL/minute. A calculated 7 mg of calcium (chelated to citrate) was lost every minute from blood to this calcium-free dialysate.

This was replaced by infusion of a 5 % calcium chloride solution into the line returning blood to the patient. The rate of calcium chloride infusion (0.5 mL/minute) ensured delivery of 7 mg of calcium/minute to blood.

In all cases dialysis was completed successfully, with no evidence of systemic anticoagulation (clotting time and APPT, measured predialysis and at hourly intervals during dialysis, remained unchanged or reduced in all patients throughout dialysis).

The clearance of urea and creatinine from blood was equivalent to that obtained with dialysis using conventional heparin anticoagulation, and no clotting was noted in the bloodlines or dialyzer during any of the 4-hour-long procedures. The extra fluid load (300-600 mL/hour) resulting from citrate infusion proved not to be a problem for the “high-efficiency” dialyzer used. None of the potential metabolic adverse effects identified by Morita et al [18] occurred.

Since this first trial, regional citrate anticoagulation protocols (not in principle different from the first) have been validated for all forms of extracorporeal RRT, including routine intermittent hemodialysis for those with CKD [20] and continuous modalities now used in critical care: continuous venous-venous hemodialysis (CVVHD) [21], continuous venous-venous hemofiltration...
(CVVH) [2, 22, 23] and continuous venous-venous hemodiafiltration (CVVHDF) [2, 24, 25].

The detail and significance of differences between citrate anticoagulation protocols for continuous RRT are discussed in a recent review [14].

Although the main impetus for the development of citrate anticoagulation was to identify a reliable alternative to heparin for a small subset of high-bleeding-risk patients, recent randomized trials [26-29] now suggest that tri-sodium citrate anticoagulation is superior to heparin anticoagulation in terms of efficacy and safety, not only for those at high risk of bleeding and those with HIT-II, but for all critically ill patients requiring continuous RRT.

Efficacy of anticoagulation in these studies is based largely on the length of time filters survive before there is evidence of clotting and they have to be replaced. Safety is based predominantly on relative bleeding risk (e.g. transfusion requirements).

In the round these studies suggest that filters anticoagulated with citrate survive longer than those anticoagulated with heparin (in one study 124 hours compared with 38 hours), and heparin anticoagulation is associated with significantly higher risk of bleeding episodes and the necessity for red-cell transfusion than citrate anticoagulation, for all critically ill patients.

The results of the largest and most recent of these [29] suggest that citrate anticoagulation is actually associated with greater chance of surviving critical illness compared with heparin anticoagulation, and that this survival benefit is not entirely explained by the reduced risk of bleeding.

In discussion of this finding the principal investigator has very recently proposed additional reasons for the observed survival benefit associated with use of citrate, but these remain speculative at this time [30].

With all these positive revelations an increasing number of intensive care units are adopting tri-sodium citrate as the standard method of anticoagulation for their patients requiring continuous RRT [14]. However, best available evidence, from a worldwide survey conducted 5 years ago [31], suggests that despite the ascendancy of tri-sodium citrate anticoagulation, unfractionated heparin remains, for the time being at least, the more frequently prescribed.

At the time of the survey 64 % of patients receiving anticoagulated continuous RRT were anticoagulated with unfractionated heparin, and 15 % were anticoagulated with tri-sodium citrate.

An obstacle to more widespread adoption of tri-sodium citrate may be the increased level of patient monitoring required to avoid the potential metabolic disturbances associated with its use [2].

Potential metabolic disturbances associated with tri-sodium citrate

Anticoagulation with tri-sodium citrate can be associated with disturbance of acid-base balance (usually metabolic alkalosis, but also metabolic acidosis), disturbance of blood calcium concentration (usually hypocalcemia but also hypercalcemia) and disturbance of blood sodium concentration (hypernatremia) [8-10, 14].

These disturbances can arise for a number of reasons but accumulation of citrate in the peripheral circulation is central in most instances. There are three main reasons why citrate may accumulate.

Firstly, the patient may be unable to metabolize (remove) citrate as efficiently as normal; citrate metabolism is diminished in those with advanced liver disease, e.g. cirrhosis, liver failure; and those with any condition associated with poor tissue perfusion (shock) [30].

Secondly, as dialysis progresses, membrane patency may be reduced and consequently less citrate-calcium complex is cleared from blood to the filtrate [8].

Finally, operational errors can lead to accidental overinfusion of tri-sodium citrate. Since citrate is the anticoagulant used to preserve blood for transfusion,
multiple transfusions during continuous RRT can contribute significantly to citrate accumulation.

Irrespective of the cause, accumulation of citrate in the peripheral circulation results in citrate chelation of circulating ionized calcium, with consequent reduced plasma ionized calcium concentration (ionized hypocalcemia). If sufficiently severe (ionized calcium < 0.8 mmol/L), this can have symptomatic effect; indeed, it may actually be life-threatening, because severe ionized hypocalcemia can cause cardiac arrhythmia and, ultimately, cardiac arrest [32].

Although plasma ionized calcium is reduced during citrate accumulation (toxicity), total calcium remains normal or maybe increased because the calcium bound to citrate is included in measured total calcium [33].

An increase in the ratio of total to ionized calcium to > 2.25-2.5:1 (normally around 2.0:1) has been found to be the most reliable signal of citrate accumulation (toxicity) [8, 14, 30, 33]; the ratio is both more sensitive and specific for citrate toxicity than plasma ionized calcium concentration alone.

Hypo- and hypercalcemia can also occur independently of any effect of citrate 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.

If tri-sodium citrate is accumulating in a patient who has the capacity to metabolize it, then metabolic alkalosis can ensue [34]. This is because bicarbonate is generated during citrate metabolism; for every mole of tri-sodium citrate metabolized, 3 moles of bicarbonate are generated [14].

The excessive bicarbonate load that causes blood pH to rise merely reflects increased citrate metabolism. Of all metabolic disturbances associated with tri-sodium citrate anticoagulation, metabolic alkalosis is probably the most common, occurring in 50 % of patients in one study [35].

Failure to metabolize citrate with resulting accumulation of citric acid is the cause of metabolic acidosis that can occur in patients receiving citrate anticoagulation and is therefore usually confined to those with advanced liver disease and/or inadequate tissue perfusion [14]. Pre-existing lactic acidosis in these patients is a likely contributory factor to development of metabolic acidosis.

The risk of increased plasma sodium (hypernatremia) associated with tri-sodium citrate anticoagulation is simply due to its high sodium content; the 4 % solution of tri-sodium citrate that has been commonly used contains 420 mmol/L of sodium [13] and is thus itself hypernatremic (cf normal plasma sodium 140 mmol/L).

In practice, the use of hyponatremic dialysis/replacement fluids usually compensates for addition of tri-sodium citrate. An alternative strategy is to use lower strength (2 %) tri-sodium citrate [20]. Hypernatremia is thus a potential, but by all accounts, rare complication of tri-sodium citrate anticoagulation.

### Monitoring tri-citrate anticoagulation

Given the attendant metabolic risks, anticoagulation with tri-sodium citrate requires careful monitoring of acid-base and plasma electrolyte balance. A minimum recommended monitoring protocol [35, 2] demands measurement of arterial blood gases, plasma ionized calcium, sodium, potassium and chloride every 6 hours. Additionally plasma total calcium should be measured daily for determination of total calcium: ionized calcium ratio (target < 2.5).

More frequent monitoring may be required for patients at high risk of citrate toxicity (e.g. those with liver disease, transfusion recipients) or following changes to the dialysis prescription (e.g. blood/fluid flow rates). Although not necessary for daily practice [36] some centers measure the post-filter plasma ionized calcium level to confirm effective anticoagulation within the circuit (target 0.25-0.35 mmol/L).

Systemically, plasma ionized calcium is often targeted to a value slightly below the normal reference range.
(1.15-1.30 mmol/L) on the grounds that most critically ill patients have a reduced ionized calcium that is thought to be protective; the suggested target value for plasma ionized calcium is 0.9-1.0 mmol/L [14].

The management of disturbances detected by this monitoring depends on the nature of the disturbance, the mode of continuous RRT employed, and detail of the citrate anticoagulation protocol, but may include any of the following: halting or reducing the rate of citrate/calcium infusion; adjusting blood flow rate; or adjusting dialysis/replacement flow rate. The principles underlying these management options are discussed in a recent review [14].

**Summary**

Regional anticoagulation with tri-sodium citrate is one of a number of alternative strategies to standard heparin anticoagulation during extracorporeal renal replacement therapy.

In contrast to heparin it is not associated with systemic anticoagulation and so is a safer alternative for patients at high risk of bleeding and patients with HIT-II.

Although citrate anticoagulation has been validated for use in conventional intermittent hemodialysis used to treat those with chronic kidney disease, it has found greatest application in continuous renal replacement therapies used in critical care to treat those with acute kidney injury.

There is an increasing body of evidence to suggest that citrate is more effective and safer than heparin in this critical care context, and a recently established trend to increased use of citrate, rather than heparin anticoagulation is set to continue.

Frequent monitoring of blood chemistry is required for safe delivery of citrate anticoagulation and the availability of reliable point-of-care test platforms that include blood gas analysis has facilitated, and will continue to facilitate the adoption of citrate anticoagulation in intensive care units around the world.

**References**


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