REVIEW

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Regional Citrate Anticoagulation: Basic Principles and Clinical Applications

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ABSTRACT

Regional citrate anticoagulation (RCA) provides effective anticoagulation within the circuit through calcium chelation during CRRT applications. Although it provides an advantage to avoid the side effects of the systemic anticoagulation, RCA application rates remain low in practice due to the fact that there are some metabolic side effects specific to citrate and the need for comprehensive protocols to perform the procedure and prevent the citrate-related metabolic derangements. Acknowledgement about the basic principles of RCA, citrate metabolism and citrate-related metabolic side effects will help the clinician to manage RCA successfully as well as recognize the risky patients on time. In this review, the basic principles and metabolic side effects of RCA will be summarized to contribute to daily practice, and the possible difficulties and pitfalls about citrate implementation will be mentioned.

Keywords: continuous renal replacement therapy, regional citrate anticoagulation, metabolic derangements, citrate accumulation, net citrate overload

Introduction

As a result of advanced technology, continuous renal replacement therapy (CRRT) is widely used in critical care settings. Although there is no significant superiority in clinical outcomes compared to conventional hemodialysis in acute kidney injury (AKI), CRRT provides effective solute and fluid clearance, especially in hemodynamically unstable patients (1). Effective anticoagulation during CRRT is mandatory for treatment success. Concomitant diseases, active bleeding or high risk of bleeding in critically ill patients affect the choice of anticoagulation and lead to early termination of treatment due to premature circuit coagulation. The Kidney Disease Improving Global Outcomes (KDIGO) recommends that citrate should be preferred over heparin for anticoagulation in CRRT unless there is a contraindication (2). Although citrate provides anticoagulation only in the extracorporeal circuit and a significant advantage in terms of avoiding anticoagulation-related systemic side effects, regional citrate anticoagulation (RCA) rates in CRRT remain low in clinical practice (3,4). The most common reasons for this situation are the presence of some citrate-specific metabolic side effects and the need for a comprehensive protocol that requires application with experienced personnel (4). In this review, the basic principles and metabolic side effects of RCA will be summarized to contribute to daily practice, and the possible difficulties and pitfalls about citrate implementation will be mentioned.

Basic Principles of RCA

When citrate is applied regionally, it binds calcium, which is a cofactor of many steps in the coagulation cascade, and prevents blood clotting within the circuit (5). It shows this effect by reducing serum ionized calcium (iCa) to 0.25-0.4 mmol/L if applied at a concentration of 3-4 mmol per 1 liter of blood (5, 6). Due to the low molecular weight of citrate, the diffusion coefficient is quite high, and this results the citrate complexes that bind calcium (CiCa) pass through the filter at a rate of 50-60% (4). It is necessary to apply calcium infusion into the systemic circulation in order to replace the calcium loss due to the hemofiltration of CiCa complexes (4). Calcium infusion rate should also be regulated to maintain the systemic iCa level within the normal range during administration (Figure 1).

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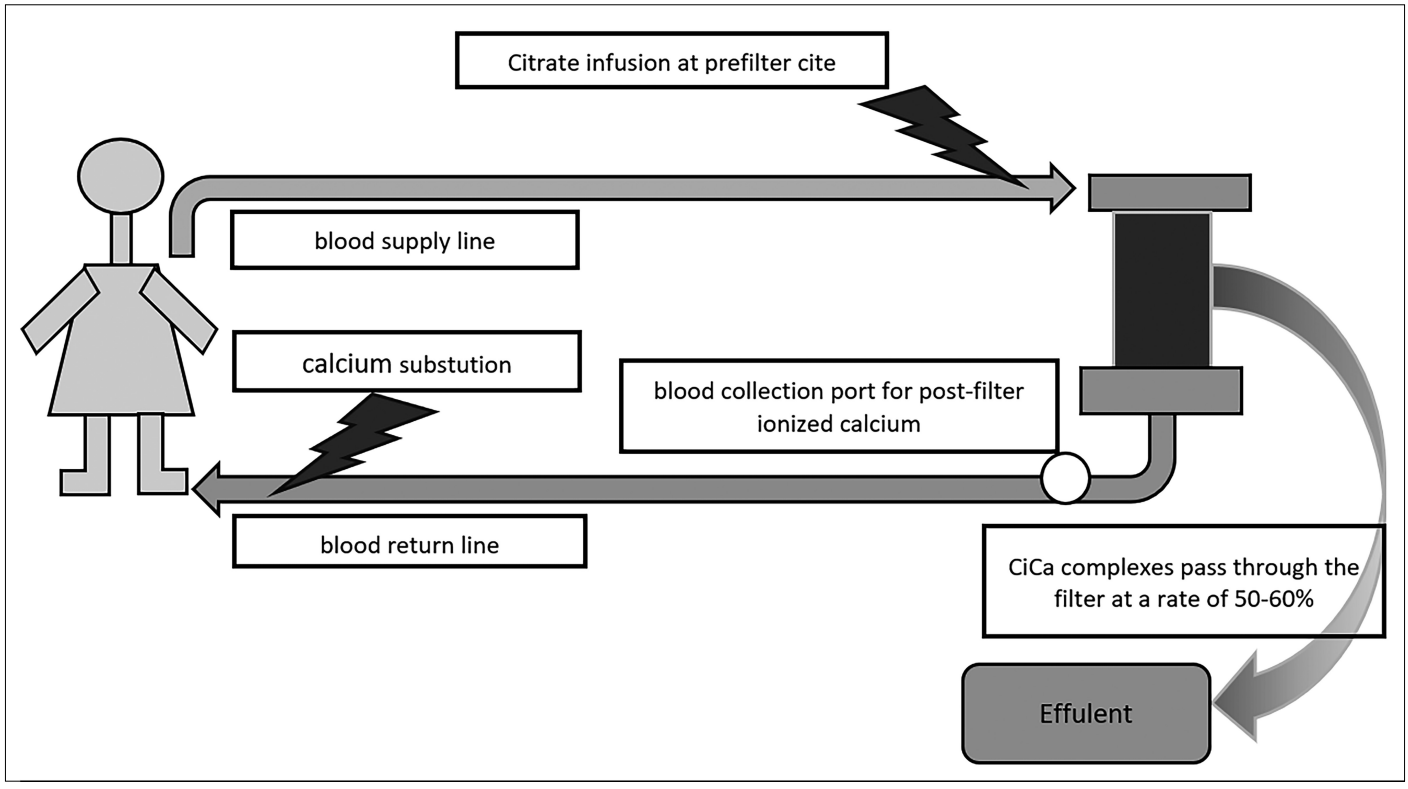

Figure 1. Shematic figure of a CRRT circuit with RCA

Protocols for RCA

There are many protocols developed to perform the RCA in a proper and safe manner (7,8). There are commercially developed automated RCA software that can be applied with both diffuse and connective techniques during CRRT, and with these systems, citrate and calcium infusion can be applied at both fixed infusion rates and titrated based on iCa levels (9). Citrate solutions can be divided into two groups as hypertonic or isotonic according to the sodium concentration within the solutions (9). There are the two different commercial citrate solutions currently used in Turkey; first one is hypertonic 4% trisodium citrate, while the other is isotonic, predilutional replacement fluid containing citrate at 18 mmol/L concentration. While hypertonic solutions are infused into the blood from a pre-filter site with a separate pump line, citrate solutions in the form of predilution replacement fluid are administered through the predilution replacement line (9). The dialysate solutions of the systems using hypertonic citrate infusion are calcium-free solutions with lower sodium and bicarbonate content than standard solutions due to the high sodium content and the buffering effect of citrate. The dialysate solutions used in RCA with isotonic predilution replacement fluid also do not contain calcium compared to standard solutions, but the bicarbonate content may be standard or lower according to the manufacturer's offerings.

Metabolism of Citrate

Citrate is an endogenous organic acid in the Krebs cycle (6). Since its two carboxylate radicals bind calcium, it can cause a mild metabolic acidosis by acting as a weak acid with the residual anionic charge (6). Under normal conditions, it is rapidly metabolized to bicarbonate, primarily in the liver, muscle and kidney (10). Apart from the bicarbonate generation, especially in case of using hypertonic citrate solution, it also provides plasma alkalinization with its high sodium concentration, that cause increased strong ion difference (SID) according to the Stewart approach (10). In clinical situations where the capacity of metabolizing citrate is exceeded or impared, CiCa complexes remain in circulation. Since there is no available assay to measure the serum citrate levels routinely, it is tried to be determined with indirect signs (6). The most commonly used marker for this purpose is the increased total serum calcium (tCa)/ iCa ratio (11,12). A ratio above 2.5 is highly indicative for ongoing citrate accumulation (6). Another commonly used signs for citrate accumulation is the gradual decrease in systemic iCa levels and the corresponding increased need for calcium substitution (12).

Metabolic Derangements Related to RCA

Metabolic acidosis and hypocalcemia

In clinical situations with impaired citrate metabolization, decreased bicarbonate generation from citrate, residual acidic effect of citrate and binding of iCa ions by CiCa complexes cause metabolic acidosis and hypocalcemia (6). This situation, defined as citrate accumulation, is the most feared complication related to RCA, especially in cases with liver failure, impaired microcirculation, shock, and aerobic glycolysis defect (6). Increased anion gap metabolic acidosis and increased serum lactate levels are not the result of impaired citrate metabolism alone, but the underlying etiology disturbs the oxygen delivery to the Krebs cycle and leads anaerobic glycolysis (6). Hypocalcemia secondary to non-metabolized CiCa complexes becomes symptomatic when iCa levels fall below 0.8 mmol/L and ptosis, tremor, hyperpnea, nausea-vomiting, prolonged QT, hypotension and cardiac arrest may develop depending on the depth of hypocalcemia (13,14).

It may be difficult to detect these findings early in unconscious and intubated patients in intensive care unit. In the presence of unexplained cardiac rhythm abnormalities, worsening of hypotension and/or increased lactic acidosis during RCA, both serum tCa and systemic iCa values should be checked quickly to exclude citrate accumulation. Although citrate accumulation is associated with high mortality, it does not occur very often in clinical practice. According to a large-scale study, the incidence of citrate accumulation was reported as 3% and its mortality was close to 100% (15). The most frequently used clinical markers for diagnose of citrate accumulation are; increased tCa/iCa ratio, low systemic iCa, metabolic acidosis with or without increased anion gap, and increasing need for calcium substitution (11,12). If citrate accumulation is diagnosed, RCA should be discontinued and an alternative anticoagulation option considered.

Metabolic alkalosis

In addition to providing regional anticoagulation as a calcium chelator, citrate has buffering effect by converting to bicarbonate through the krebs cycle in the body, predominantly in the liver, muscle and kidney (16). The bicarbonate gain of citrate provides has a positive effect in correcting metabolic acidosis related to AKI. On the other hand, excessive bicarbonate generation exceed the base deficient may cause metabolic alkalosis (16). Metabolic alkalosis is more common than citrate accumulation, and called net citrate overload (6). In net citrate overload, it is not expected that increased tCa/iCa ratio or decreased iCa levels as iCa is released to plasma secondary to metabolized CiCa complexes (6). In such situation, the dialysate or replacement flow rate is increased in order to reduce the amount of citrate returned to the patient to correct the existing metabolic alkalosis, thus eliminating the CiCa complexes by ultrafiltration (9). The amount of citrate applied to the circulation can also be reduced by lowering either the blood flow rate or the citrate concentration per blood flow (9).

Other electrolyte disturbances related to RCA

There is a risk of developing hypernatremia due to the use of hypertonic solutions with high sodium content such as 408 mmol/L as a source of citrate (17). The manufacturer recommends low sodium content dialysate solutions during RCA in order to minimize this effect, this situation seems to be very low in clinical practice (18). Since the sodium content in isotonic citrate replacement fluids is 140 mmol/L, it does not carry an increased risk of hypernatremia.

Due to the affinity of citrate to divalent cations, the loss of chelates formed by citrate by binding magnesium through ultrafiltration may lead to hypomagnesemia in the patient (6,16). Measuring the serum magnesium level at regular intervals and making the appropriate replacement on time will prevent hypomagnesemia-related side effects.

Although hypokalemia and hypophosphatemia are not specific RCA-related electrolyte disorders, effective solute clearance linked to the extended filter life provided by RCA and failure to meet the daily electrolyte requirement to compensate for the loss with ultrafiltration may lead to overt hypokalemia and hypophosphatemia (19,20). Upon return of elevated serum potassium and phosphate levels to the normal range in the presence of AKI, the use of dialysate solutions containing potassium and phosphorus at various concentrations will prevent the development of hypokalemia and hypophosphatemia.

Contraindications for RCA

Decreased lactate clearance was demonstrated in cirrhotic patients in clinical studies on citrate pharmacokinetics and metabolism, since the liver plays a major role in its metabolism (21). Although the KDIGO guidelines define severe hepatic failure as a contraindication for RCA, many prospective studies have shown that RCA can be administered safely and effectively in the presence of liver dysfunction (22-24). In a recent meta-analysis on this subject, it has been reported that RCA can be safely applied in CRRT with close monitoring of acid-base status and serum electrolyte levels in liver failure (25). The fact that no liver function test was found to be directly related to impaired lactate clearance, lower rates of citrate toxicity were encountered contrary to expectations in clinical studies in liver patients and case reports about RCA application in pediatric cases with specific genetic defects of the Krebs cycle was successfully applied without causing any toxicity, it seems that citrate can be eliminated by another metabolic pathway other than the Krebs cycle (21, 26-28). In this respect, it is suggested that citrate can also be metabolized via the Cori cycle, an inducible metabolic pathway found in all cells (26,27). Some authorities on this assumption; argues that the main determinant of citrate accumulation is microcirculation rather than liver function (26,29). Especially in shock situations accompanied by multi-organ failure that may cause high lactate, the risk of citrate accumulation should be monitored closely, and in case of an increase in lactate according to baseline, it should be decided whether to continue RCA in accordance with the benefit-harm assessment (15). In addition, due to mitochondrial dysfunction in metformin intoxication, extreme caution should be exercised in RCA (9). It is also an important point to keep in mind that in hypercapnic patients with spontaneous breathing, excess production bicarbonate related to citrate may increase carbon dioxide production and compromise respiratory status (9).

Pitfalls in RCA

Blood gas analyzers are frequently used to monitor the iCa level during RCA. The reliability of the blood gas analyzer device used in measuring the iCa level below the normal limits is an important point that the units applying RCA should pay attention (9). Especially in iCa levels below the normal limits, the use of devices with poor measurement reliability may lead to making the recommended changes in citrate protocols more frequently according to the post-filter iCa result, resulting in a higher incidence of citrate-related metabolic complications (30). Another issue to be considered at this point is that blood gas samples must be loaded into the device with appropriate injectors. Instead of liquid heparin blood gas injectors, commercial electrolyte-balanced dry heparin injectors should be preferred as they will increase the measurement reliability, especially in order to get rid of the dilution effect of liquid heparin (31,32).

The recommended tCa/iCa ratio for citrate accumulation may have some limitations in intensive care unit according to the Boer approach (33,34). Especially albumin, phosphate, pH, disease

severity and lactate levels have some effects on iCa and may cause false positives or negatives readings (33,35-39). Therefore, if citrate accumulation is suspected, the patient's other clinical signs and hemodynamic status should be evaluated together with the tCa/iCa ratio (15).

Tips to Consider in Clinical Practice

Whether citrate provides effective anticoagulation during RCA should be monitored by post filter iCa levels. For this purpose, it is mandatory to take a blood gas sample from the return line of the filter. After determining the citrate dose according to post-filter iCa levels, it is regularly checked every 6 to 8 hours during the CRRT (9). The calcium substitution should be adjusted with the systemic iCa levels, checked at regular intervals (40). Another important point to note here is that the blood gas sample for monitoring systemic iCa should be driven from a region not close to the calcium infusion line. Otherwise, the dose adjustment to be made according to the systemic iCa levels that will be falsely high, may lead to hypocalcemia over time.

In addition to citrate dose adjustment, it is very important to regularly check and interpret the results of systemic blood gas analysis for a citrate-related metabolic complication. For this purpose, pH, HCO_3 and lactate level should be evaluated in terms of any metabolic acidosis or alkalosis (Table 1). In the presence of metabolic alkalosis, net citrate overload should be considered and the amount of citrate return to the systemic circulation should be decreased and/or citrate clearance should be increased by adjustment of effluent dose (9). In the presence of metabolic acidosis, ongoing metabolic acidosis due to insufficient buffering or citrate accumulation should be considered. In the first scenario, the citrate is fully metabolized to bicarbonate but the amount of metabolised citrate is insufficient buffer to patient's demand. The right intervention is to increase the citrate dose return to patient by increasing either the blood flow rate or the citrate concentration per blood flow (9). For this purpose, the dialysate and/or replacement flow rate can be decreased to reduce the filtration of CiCa complexes (9). In this way, the total effluent dose calculated for CRRT will be reduced leading to a reduction in solute clearance. The second scenario is the most feared metabolic complication related to RCA, where citrate cannot be metabolized. Since this condition is usually caused by arterial hypoxemia and decreased tissue perfusion, the increased lactat level is also often observed. In citrate accumulation, there is an increase in the tCa/iCa ratio, a decrease in iCa, and an increase in the required calcium substitution with metabolic acidosis (9). Since the first observed sign before the development of overt metabolic acidosis is gradually increasing calcium substitution dose, in the presence of such a situation, the systemic iCa level should be checked and the patient should be re-evaluated for possible accumulation by calculating the tCa/iCa ratio (12). If citrate accumulation is diagnosed, RCA should be terminated and CRRT should be continued with alternative anticoagulation options, and thus the CiCa complexes, remaining in the circulation should be removed by hemofiltration (9).

Frequent control of iCa, serum electrolyte and acid-base status combined with a comprehensive RCA protocol will prevent the development of the metabolic complications detailed above (17). The training of health personnel is also very important in terms of increasing compliance with the protocols. Although there is no absolute contraindication for RCA application, it should be noted that impaired liver functions, arterial hypoxemia and decreased tissue perfusion carry the highest risk for citrate accumulation (12).

Table 1. Approach to common metabolic derangements related to regional citrate anticoagulation (RCA)

	Citrate accumulation	Insufficient buffering	Net citrate overload
Mechanism	Decreased citrate metabolism	Insufficient buffer delivery	Excessive bicarbonate generation exceed the base deficient
Systemic blood gas results			
pH status	Metabolic acidosis	Metabolic acidosis	Metabolic alkalosis
HCO_3	⬇	⬇	⬆
Lactate	⬆	Normal	Normal
iCa++	⬇	Normal	Normal
Total calcium	⬆	Normal	Normal
tCa/iCa ratio	⬆	Normal	Normal

Conclusion

Preferring regional citrate application in CRRT is advantageous to avoid anticoagulation-related systemic side effects and provide an effective anticoagulation in the extracorporeal circuit. The fact that there are some metabolic complications specific to citrate administration and the need for a comprehensive protocol with experienced personnel causes RCA utilization rate to remain low. Frequent control of iCa, serum electrolyte and acid-base status combined with a comprehensive RCA protocol will prevent the development of the metabolic complications. Preferring citrate over heparin for anticoagulation in CRRT applications, as recommended by KDIGO, will provide effective solute and fluid clearance with longer filter time. Although there is no absolute contraindication for RCA application, it should be noted that impaired liver functions, arterial hypoxemia and decreased tissue perfusion carry the high risk for citrate accumulation.

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