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CASE REPORT

Artificial Kidney / Dialysis

Regional citrate anticoagulation and influence of recirculation on ionized calcium levels in the circuit

Anais Degraeve[1] · Etienne Danse[2] · Pierre-François Laterre[1] · Philippe Hantson[1] · Alexis Werion[1]

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Abstract
Regional citrate anticoagulation is now widely used during continuous renal replacement therapy (CRRT), and especially in patients at risk for hemorrhagic complications. A close monitoring is required to avoid citrate overload, leading to metabolic alkalosis or citrate intoxication causing metabolic acidosis. This case report describes a dysfunction of the regional citrate anticoagulation due to the development of a deep vein thrombosis close to the site of insertion of the venous CRRT catheter. The result was a local recirculation in the circuit with a local citrate overload (acidosis and non-measurable calcium). In the patient's blood samples, the [$calcium_{total}/Ca^{2+}{}_{systemic}$] ratio remained normal as a proof of local citrate accumulation without systemic effects. Initially, CRRT remained effective, but due to the progressive decrease of serum creatinine and cystatin C clearance, the site of catheter insertion was changed.

Keywords Regional citrate anticoagulation · Recirculation · Continuous renal replacement therapy

Introduction

We present here a rare case of dysfunction of regional citrate anticoagulation (RCA) during CRRT. The patient developed a deep iliac venous thrombosis close to the site of insertion of the CRRT catheter, which caused recirculation in the CRRT circuit and local citrate overload without systemic effects in the patient. A similar case had already been described in a young patient after the reversion of the lines of a dual-lumen dialysis catheter in the femoral position [1].

Case report

A 61-year-old woman stayed in the intensive care unit (ICU) after a liver transplantation. Her medical past history included type 1-diabetes, a first liver transplantation 27 years ago for autoimmune cirrhosis, and a second transplantation 24 years ago for chronic ischemic liver damages. She underwent a third liver transplantation because of a persistent and invalidating encephalopathy. In the immediate post-operative course, serum BUN was 7.8 mmol/L (NV: 2.5–8.3) and creatinine 83.1 µmol/L (NV: 53–114.9).

Twelve days after admission, she developed an acute kidney failure with oliguria (145 mL/24 h), hyperkaliemia up to 7 mmol/L (pH 7.48, bicarbonate 25 mmol/L) and low serum creatinine clearance (11 mL/min), with BUN 31.3 mmol/L and creatinine 194.5 µmol/L. She required CRRT for metabolic disorders. In view of multiple recent hemorrhagic complications, regional citrate anticoagulation (RCA) was chosen for continuous venovenous hemofiltration with Aquarius dialyzer (Nikkiso medical®). The insertion of a right femoral venous dual-lumen hemodialysis catheter (8 Fr, 20 cm) had been guided by echography. The blood flow was set at 150 mL/min. Citrate was administered before the filter (AN-69® filter; 0.6 m^2), and the pre-dilution and post-filter fluid flow with Prismocal® was 1000 mL/h each.

The RCA was conducted according to our local protocol. Namely, the targets values for ionized calcium (iCa^{2+}) are 0.3–0.34 mmol/L after the dialysis membrane, and 1.05–1.2 mmol/L in systemic sample. Citrate 13% is infused at an initial rate of 50 mL/h and then adapted to the values

✉ Philippe Hantson
philippe.hantson@uclouvain.be

[1] Department of Intensive Care, Cliniques Universitaires Saint-Luc, Avenue Hippocrate, 10, 1200 Brussels, Belgium

[2] Department of Radiology, Cliniques Saint-Luc, Université Catholique de Louvain, 1200 Brussels, Belgium

of iCa^{2+} after the filter. When iCa^{2+} is below 0.3 mmol/L, the citrate infusion rate is reduced by 10%, and increased by 10% with iCa^{2+} above 0.34 mmol/L. Calcium chloride is reinfused in a venous central line (and not after the filter) at an initial rate of 5 mL/h that is adapted to the target values of systemic iCa^{2+}. Monitoring of iCa^{2+} is performed routinely every 4 h or more frequently, following changes in citrate infusion. According to this protocol, the initial infusion rate was 50 mL/h for citrate and 6 mL/h (corresponding to 3.3 mmol Ca^{2+}) for calcium chloride.

Twelve days after insertion, a high venous pressure was noted in the circuit together with clotting. A few hours later, iCa^{2+} became non-measurable on the venous line. We replaced the catheter (through a trans-catheterization technique), changed the circuit and also the machine to exclude an obstruction of the catheter, a stenosis or a fault in the circuit. Despite the progressive reduction of citrate administration (to 20 mL/h, or even stopped for several hours), iCa^{2+} remained non-measurable in the circuit. Total calcemia was normal and no more intravenous calcium supplementation was required. The results of the samples drawn from the arterial or venous line, from the CRRT catheter or from the CRRT machine, are displayed in Table 1. The association of acidosis and non-measurable iCa^{2+} in the circuit demonstrated local citrate overload; the [$calcium_{total}$/$Ca^{2+}{}_{systemic}$] ratio was (1.88/1.10 =) 1.71.

The abdominal vascular ultrasound examination (Fig. 1, left) revealed that the flux in the right iliac vein and in the catheter had the same cranio-caudal direction. The abdomen computed tomography (CT) (day 17) with contrast administration (Fig. 1, right) demonstrated the presence of an iliac venous thrombosis explaining the recirculation.

Recirculation was estimated according to the formula based on blood urea nitrogen (BUN) measurement: $R = (S_{BUN} - A_{BUN})/(S_{BUN} - V_{BUN})$, where R is the recirculation rate, S_{BUN} is the systemic value of BUN, A_{BUN} is the pre-filter sample and V_{BUN} is the post-filter sample (Table 2) [2]. The recirculation rate was estimated at 96%.

As indicated in Table 2, the occurrence of recirculation resulted in a progressive decrease of CRRT efficacy. Eighteen days after catheter insertion, serum creatinine clearance was 17 mL/min/1.73 m^2 and serum cystatin C clearance 14 mL/min/1.73 m^2.

Despite technical difficulties and coagulation disorders, the site of catheter insertion was finally changed for the right internal jugular vein, with a subsequent recovery of CRRT efficacy. The patient ultimately died one month later from complications unrelated to CRRT.

Table 1 Evolution of ionized calcium (iCa^{2+}) on samples obtained on day 12

Hour	16h58	17h19	17h22	17h48	17h51
Sample site	Systemic	CRRT venous line	CRRT arterial line	CRRT catheter arterial lumen	CRRT catheter venous lumen
Results	pH 7.38 iCa^{2+} 1.10 HCO_3^- 14	pH "abnormal" iCa^{2+} NM HCO_3^- NM	pH "abnormal" iCa^{2+} NM HCO_3^- NM	pH "abnormal" iCa^{2+} NM HCO_3^- NM	pH 6.6 iCa^{2+} NM HCO_3^- 8

CRRT continuous renal replacement therapy, *iCa^{2+}* mmol/L, *K^+* mmol/L, *$HCO3^-$* bicarbonate mmol/L, *NM* non-measurable, *abnormal* out of range for analyzer

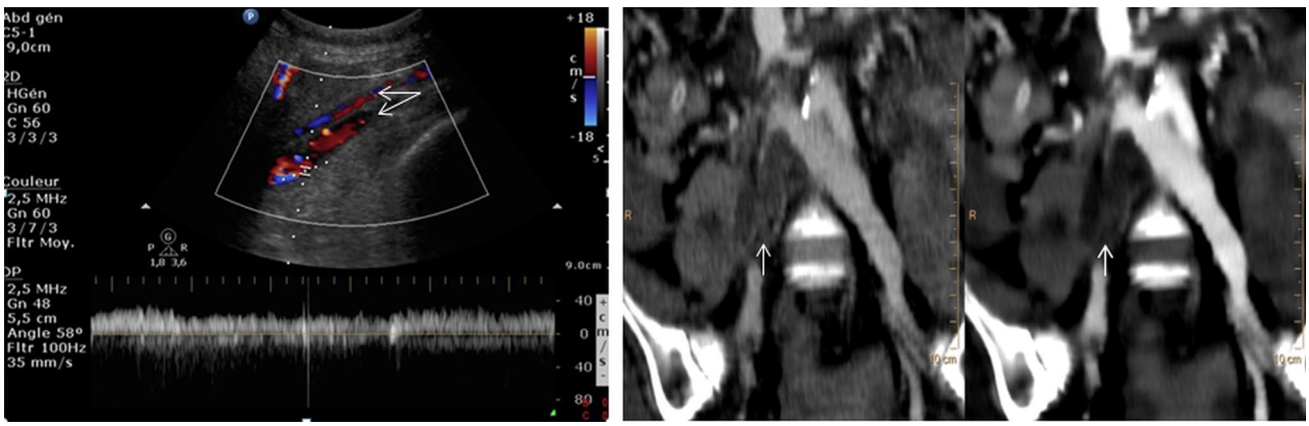

Fig. 1 Left: cranio-caudal flux (orange color) in the CRRT catheter and in the right iliac vein (double arrow) on abdominal Doppler ultrasound examination. Right: frontal imaging of the deep venous (iliac) thrombosis (arrow) on abdomen computed tomography

Table 2 Daily serum urea, creatinine, potassium and bicarbonate concentrations, time scale from catheter insertion

	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17 a.m.	Day 17 p.m.	Day 18	Day 19
Systemic BUN (mmol/L) (2.5–8.3)	9.2	11.8	13.8	16	21.6	24.6	25.5	28.1	20
Systemic creatinine (μmol/L) (53–114.9)	154.7	166.2	166.2	173.3	190.9	235.1	251.9	259.9	150.3
For estimation of recirculation									
BUN arterial line							17		
BUN venous line							22		
Creatinine arterial line							52.1		
Creatinine venous line							55.7		
Potassium (mmol/L) (3.5–5.0)	4.56	4.17	4.56	4.52	4.62	4.94		5.35	3.57
Bicarbonate (mmol/L) (22–29)	15	14.1	15.1	11.4	11.2	15.6		15.1	20.9
Total calcium (mmol/L) (2.2–2.55)	2.41	2.47	2.44	2.28	2.33	2.36		2.8	2.30

Discussion

The use of citrate provides an efficient local anticoagulation without increased risks of bleeding (see [3, 4] for review). This can be reached through the high affinity of citrate to calcium, essential in the coagulation cascade. Citrate calcium complexes (CCC) are mainly eliminated into the dialysate. The remaining CCC are metabolized into bicarbonate, sodium and calcium mainly by the liver.

To be efficient, ionized calcium after the filter must be monitored. The target value may vary according to different protocols, but usually fits between 0.2 and 0.35 mmol/L. Below this level, there is a risk of CCC accumulation, and above, anticoagulation will be insufficient [4].

This technique is associated with different complications: hypocalcemia, acid–base disturbance (both metabolic alkalosis or acidosis), hypernatremia, …

To avoid hypocalcemia, accurate metabolization of CCC and systemic calcium infusion are mandatory. Metabolic alkalosis may be the consequence of citrate overload, as a result of an augmented metabolization. The treatment consists of increasing the part of dialyzable CCC, by decreasing the blood flow or increasing the dialysate flow rate. Metabolic acidosis can be lethal by altering myocardial contractility and/or inducing vasoplegia. It happens when not catabolized CCC are overloading. To prevent this, the level of CCC must be monitored. In the absence of a routine dosage of CCC, this level can be estimated through the total/ionized calcium ratio. If this ratio is higher than 2.5 or presents an increasing trend, the risk of acidosis is increased.

In our case, blood gas analysis showed non-measurable ionized calcium justifying a decrease of citrate infusion. After multiple episodes of filter clotting, severe acidosis was documented after the filter explaining non-measurable calcium. Indeed, blood gas analyzers can evaluate ionized calcium only in a pre-defined range of pH. In the absence of systemic consequences, the acidosis can be explained by a local accumulation of non-metabolized CCC. Local recirculation was then searched and a deep venous thrombosis was diagnosed close to the tip of the CRRT catheter.

The recirculation rate estimated by the above-mentioned formula was 96% and values higher than 10% are usually considered as significant according to different studies. We can suppose that in ICU patients with altered urea production, this test could be biased. In the present case, a similar result was noted when cystatin C was used as a biomarker of recirculation. Other techniques evaluating catheter recirculation are available, but require interventional procedures (glucose infusion test, thermodilution techniques, colorimetric measures (mainly for laboratory use),…) [5–7]. Recirculation phenomena may lead to low calcium levels in the circuit, but to high calcium levels in the patient if an excessive calcium load is provided separately from the circuit.

A similar case had been described in a young patient during the reversion of the lines of a dual-lumen dialysis catheter in the femoral position [1].

In conclusion, through this observation of dysfunction of RCA, we recommend evaluating the possibility of recirculation in any patient with signs of local citrate accumulation without systemic consequences.

Compliance with ethical standards

Conflict of interest All the authors have no conflict of interest to disclose.

Informed consent A written consent was obtained from the relatives.

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