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Case Report

Novel Use of Regional Citrate Anticoagulation for Ultrafiltration Circuit in a Neonate with Severe Ebstein's Anomaly and Intracranial Hemorrhage

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Keywords

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- Continuous venovenous hemofiltration
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- Regional citrate anticoagulation

Abstract

Background: Renal Replacement Therapy (RRT), even continuous veno-venous hemofiltration (CVVH), is often not well tolerated in hemodynamically unstable patients. Ultrafiltration (UF) using the Aquadex™ system has emerged as a potential alternative therapy for fluid removal in critically ill pediatric patients. UF, like CVVH, traditionally requires systemic anticoagulation, putting patients at risk for hemorrhage, and precluding its use for fluid removal in patients who have had bleeding complications.

Case: In this report, we present a neonate with complex congenital heart disease, intracranial hemorrhage and acute kidney injury (AKI) who received UF using the Aquadex™ system with regional citrate anticoagulation (RCA) instead of the usual unfractionated heparin.

Conclusions: To our knowledge, we describe the first case of the successful use of citrate for anticoagulation for UF using the Aquadex™ system. Given that this novel modality for fluid removal is most useful in critically ill children who are commonly at risk for bleeding complications, RCA may prove to be a viable and important alternative to systemic anticoagulation with heparin in this population.

ABBREVIATIONS

RRT: Renal Replacement Therapy; CCVH: Continuous Venovenous Hemofiltration; UF: Ultrafiltration; AKI: Acute Kidney Injury; RCA: Regional Citrate Anticoagulation; PCRRT: Pediatric Continuous Renal Replacement Therapy; BFR: Blood Flow Rate

INTRODUCTION

Fluid overload in critically ill children is associated with increased risk of morbidity and mortality. RRT is the gold standard treatment for fluid overload when conventional diuretics fail, and early initiation of RRT has been associated with improved outcomes [1]. Unfortunately, RRT, even CVVH, is often not well tolerated in hemodynamically unstable pediatric patients. UF using the Aquadex™ system has emerged as a potential alternative therapy for fluid removal in critically ill pediatric patients [2,3]. Like CVVH, UF traditionally requires systemic anticoagulation, putting patients at risk for hemorrhage, and precluding its use for fluid removal in patients who have had bleeding complications. Based on experience using RCA for CVVH, we hypothesized that this strategy would be effective for UF while minimizing risk of bleeding. We present a case where RCA was used as anticoagulation for UF using the Aquadex™ system in a hemodynamically unstable pediatric patient with a history of intracranial hemorrhage.

CASE PRESENTATION

The patient is a female infant with the pre-natal diagnosis of Ebstein's anomaly with severe tricuspid regurgitation, pulmonary valve atresia, and significant cardiomegaly with severe lung hypoplasia. The patient was delivered via C-section for hydrops fetalis and non-reassuring fetal heart tracing at 36 weeks gestation. Her post-natal course was complicated by severe hypoxemia and respiratory and metabolic acidosis, as well as atrioventricular re-entrant tachycardia. The patient's condition stabilized with high frequency oscillation ventilation, fluid resuscitation, correction of metabolic acidosis, inotropic support, vasopressor support, and arrhythmia control. Nonetheless, the patient developed acute kidney injury with fluid overload refractory to treatment with

conventional diuretic therapy and fenoldopam. Due to ongoing hemodynamic instability and declining respiratory status, peritoneal dialysis was attempted, but this was not tolerated due to hypoxemia and hypotension associated with abdominal distension. Consequently, the decision was made to proceed with UF using the Aquadex™ system. Head ultrasound was normal at initiation of therapy. Standard systemic anticoagulation with unfractionated heparin was initially utilized. The patient achieved significant negative fluid balances on each day of UF therapy. After four days, UF was discontinued due to the appearance of hemorrhagic transformation of periventricular leukomalacia on surveillance head ultrasound. Retrospective review of serial head ultrasound studies showed that subtle findings of periventricular leukomalacia had been present prior to initiation of UF. Over the next two weeks, the patient continued to achieve a negative fluid balance with urine and peritoneal drain output, but respiratory support could not be weaned. The patient's clinical status began to worsen, and fluid overload recurred despite aggressive diuretic therapy, so UF was reinitiated using RCA in the setting of the previously-noted hemorrhagic transformation of periventricular leukomalacia.

Most Pediatric Continuous Renal Replacement Therapy (PCRRT) protocols recommend initiating RCA, using anticoagulant citrate dextrose solution A, with a citrate infusion rate of 52.5 ml/hour, or 1.5 times the blood flow rate (BFR). The patient developed evidence of citrate toxicity, and the citrate infusion was decreased to 1.0 times the BFR, and then further decreased to 0.3 times the BFR.

Based upon established PCRRT protocols, the calcium chloride infusion had been initiated at 0.326 mEq/kg/hr (0.163 mmol/kg/hr) and as the citrate infusion rate was decreased, the calcium infusion rate was also decreased to 0.11 mEq/kg/hr (0.06 mmol/kg/hr). Therapy with UF was continued for 22 hours, but the patient's hemodynamic response to decreased intravascular fluid volume did not allow for significant fluid removal. Notably, there was no evidence of progression of the intracranial hemorrhage during the period of therapy on serial ultrasound studies. In addition, the extracorporeal circuit itself functioned well, with no evidence of thrombosis. In light of the inability to wean respiratory support and the patient's declining clinical status, the parents elected to withdraw support.

DISCUSSION

Ultrafiltration using the Aquadex™ system has emerged as a potential modality for fluid removal in critically ill pediatric patients [2,3]. One of the limitations of this therapy is the need for systemic anticoagulation, with the associated risk of bleeding complications. RCA has been used in CVVH as an alternative to systemic anticoagulation in an attempt to reduce the risk of hemorrhage, but the use of RCA has not previously been described with UF using the Aquadex™ system.

Use of RCA has several potential benefits over systemic unfractionated heparin anticoagulation for RRT. Morabito et al showed that in adult cardiac surgical patients requiring CVVH, those who received RCA had lower transfusion rate, higher platelet count, and higher anti-thrombin type III activity as compared to those patients receiving standard therapy with unfractionated heparin [4]. In addition, several studies have demonstrated that RCA increases extracorporeal circuit life by up to two times, as compared to unfractionated heparin anticoagulation [5-9]. As a result, use of RCA has the potential to minimize circuit downtime, which is associated with increased transfusion requirements and a reduction of treatment efficacy, both of which potentially increase costs of care [10]. Another benefit of RCA is the avoidance of heparin induced thrombocytopenia, which is an important consideration in patients with congenital heart disease, who often require subsequent heparin exposure during cardiac procedures [9].

Calcium is a necessary part of the coagulation cascade, required for activation of most vitamin K dependent factors (VII, IX, X) and factor XII, as well as platelets [11]. Citrate is an effective anticoagulant due to its ability to chelate calcium and inhibit these factors. When administered pre-filter in a CRRT circuit, it binds ionized calcium, creating a calcium citrate complex and lowering the free ionized calcium. Systemic anticoagulation is avoided by extracorporeal filtration and metabolism in the body. Similar to filters used for CVVH, the Aquadex™ filter has a sieving coefficient of approximately 0.96 for particles up to 1,355 g/mol. Citrate molecules are small, 258.06 g/mol, and are therefore freely filtered and lost in the ultrafiltrate (Baxter Corporation, Minneapolis, Filter specifications). In addition, citrate has a relatively short systemic half-life, undergoing metabolism within mitochondria of the liver, skeletal muscle, and kidneys [7,11]. Calcium chloride is administered post-filter or directly to the patient to counter hypocalcemia induced by loss of chelated calcium in the ultrafiltrate. When utilizing RCA for CVVH, it is standard to monitor anticoagulation level by measuring pre- or post-filter ionized calcium, with a target of less than 3.5mmol/L [11]. Although measurement of citrate level is not routinely used [10], extracorporeal ionized calcium levels below 0.35mmol/L correspond to extracorporeal citrate levels of 4-6mmol/L [11]. We did not draw post-filter ionized calcium samples from the circuit, as manufacturer recommendations suggested that blood sampling from circuit access ports increases the risk of circuit thrombosis. Samples for ionized calcium were therefore obtained directly from the patient, with a target of 0.9-1.0mmol/L [11].

Despite citrate filtration and hepatic citrate metabolism, calcium disturbances remain an important concern when using RCA, with a reported incidence of citrate toxicity of approximately 3% [12]. Citrate intoxication, also known as "citrate lock", occurs due to its accumulation in the bloodstream, leading to low ionized calcium. It is characterized by elevated total serum calcium, as the citrate-calcium complex is included in total serum calcium measurement, in addition to metabolic acidosis, and an increased anion gap [9]. Therefore, electrolytes and acid-base status must be monitored closely during RCA. Hypocalcemia related to citrate toxicity can result in decreased cardiac contractility and vascular tone, ECG changes and arrhythmias, and if severe, impaired coagulation [13]. Factors contributing to citrate accumulation include impaired liver function, arterial hypoxia, and reduced tissue perfusion [12]. Citrate toxicity is likely when the ratio of total serum calcium to ionized calcium, both measured in mmol/L, exceeds 2.5 [11]. The treatment for citrate toxicity associated with CVVH anticoagulation is to reduce or stop the citrate infusion, increase the dialysate flow rate in CVVH, and increase the calcium infusion rate [9].

In the case described above, anticoagulant citrate dextrose solution A was utilized. This is one of the most commonly available citrate solutions and contains 224 mmol/L of sodium, 74.8 mmol/L of citrate, and 38 mmol/L of citric acid (2.13% citrate ion). Our experience was similar to that described by Morgera et al, in which lower citrate infusion rates than recommended in standard protocols achieved adequate anticoagulation [11]. We ultimately achieved adequate anticoagulation while avoiding citrate toxicity at a citrate dose of 1.13 mmol/L of circuit blood flow [14]. In addition, our experience was similar to previous reports which demonstrated that infants and children require higher doses of calcium during RCA than adults [4,8].

CONCLUSIONS

To our knowledge, we describe the first case of the successful use of citrate anticoagulation for UF using the Aquadex™ system. Given that this novel modality for fluid removal is most useful in critically ill children who are commonly at risk for bleeding complications, RCA may prove to be a viable and important alternative to systemic anticoagulation with heparin in this population.

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