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Impact of daytime continuous veno-venous haemofiltration on treatment of paediatric tumour lysis syndrome

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Abstract

Objective: Continuous renal replacement therapy (CRRT) is well suited for treating metabolic abnormalities and renal insufficiency associated with tumour lysis syndrome (TLS). However, there is controversy regarding the choice of time for CRRT, the selection of CRRT models, and methods of decreasing complications of CRRT. This study aimed to evaluate the efficacy and outcomes of daytime continuous veno-venous haemofiltration (CVVH) for treating paediatric TLS.

Methods: The clinical features, technique-related complications, and prognosis were prospectively analysed in eight paediatric patients with TLS who were supported by daytime CVVH in West China Second University Hospital, Sichuan University from January 2007 to July 2016.

Results: Seven patients were boys and one was a girl. All of the patients had hyperphosphataemia, and there were four cases of hyperkalaemia, four cases of hyperuricaemia, and two cases of hypocalcaemia. All of the patients received one to 10 CVVH treatments. Urine output, renal function, serum uric acid levels, and potassium, phosphate, and calcium levels returned to normal in all of the patients, but recovery of renal function was relatively slow. No significant adverse reactions were observed. All of the patients recovered and were discharged.

Conclusion: Daytime CVVH is a safe and effective treatment for paediatric TLS.

Keywords

Tumour lysis syndrome, children, continuous veno-venous haemofiltration, daytime, continuous renal replacement therapy, acute kidney injury, hyperphosphataemia

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Introduction

Tumour lysis syndrome (TLS) is a rare, but potentially life-threatening complication, of neoplasms, especially haematological malignancies.[1] TLS is characterized by rapid onset of hyperuricaemia, hyperkalaemia, hypocalcaemia, hyperphosphataemia, and acute kidney injury (AKI) following rapid release of intracellular material from lysing malignant cells.[2] This syndrome can be life threatening, and it occurs during the early phase of diagnosis and treatment of high proliferative malignant neoplasms. TLS has an incidence of 1.1% to 6%.[3]

Management of TLS requires hydration, fluid balance, electrolytes, and correction of hyperuricaemia.[4] Despite rasburicase use,[5] blood purification still ranges between 1.5% for paediatric patients and 5% for adult patients. The purposes of blood purification are to augment clearance of potassium, phosphate, and uric acid, to correct any considerable metabolic acidosis, and to provide appropriate therapy for associated AKI.[6] Because peritoneal dialysis does not adequately clear uric acid, its routine use is not recommended for TLS.[7] Intermittent haemodialysis is preferred to clear uric acid, but potassium rebound limits its efficacy.[8] Because TLS originates from a continuous release of potassium, phosphorus, and uric acid, continuous renal replacement therapy (CRRT) is preferred to intermittent haemodialysis to reduce the risk of rebound hyperkalaemia and hyperphosphataemia.[9–14]

However, there is controversy regarding the choice of time for CRRT in critical patients, the selection of CRRT models, and the methods of decreasing complications of CRRT for TLS.[4,6,15] Continuous veno-venous haemofiltration (CVVH) is an effective form of renal replacement therapy for AKI. CVVH offers greater haemodynamic stability and better volume control than conventional haemodialysis in critically ill, hypotensive patients. Despite the possible benefits, application of CVVH in the intensive care unit has several disadvantages, including intensive nursing requirements, continuous anticoagulation, patient immobility, and expense.[16] Recently, prolonged (daily) intermittent renal replacement therapies have been proposed as intermediate forms of therapy between continuous and intermittent renal replacement therapy.[15,17] Several trials showed no difference between sustained low-efficiency dialysis and CVVH in terms of mortality.[15,17] This study aimed to investigate the efficacy and outcomes of daytime CVVH for treating paediatric TLS.

Methods

Study design

Because paediatric TLS is rare and occurs unpredictably, we performed a non-blinded, uncontrolled study of children who were hospitalized with severe TLS at the West China Second University Hospital, Sichuan University, China. The study period was from January 2007 to July 2016.

Subjects

Hospitalized children with TLS who had not responded to conventional treatments were selected for daytime CVVH on a patient-by-patient basis by the treating paediatrician. Written informed consent was obtained for all patients. TLS was defined in accordance with the Cairo–Bishop classification.[18] Laboratory TLS was confirmed if the patients had at least two of the following clinical features 3 to 7 days after initiating chemotherapy: serum uric acid levels $\geq$476 μmol/L or 25% higher than the previous level, serum potassium levels $\geq$6.0 mmol/L or 25% higher than the previous level, serum phosphate levels $\geq$1.45 mmol/L (in adults) or 25% higher

than the previous level, and serum calcium levels $\leq$1.75 mmol/L or 25% less than the previous level. Clinical TLS was confirmed if the patients fulfilled the laboratory TLS criteria and exhibited at least one of the following clinical features: (1) serum creatinine levels $\geq$1.5-fold the upper limit of normal serum creatinine levels, (2) arrhythmia/sudden death, and (3) epileptic seizure.

Conventional treatments

All chemotherapy regimens were discontinued. TLS patients received a total of 0.2 mg/kg·d rasburicase to reduce uric acid production. Furosemide was administered at 1 to 2 mg/kg two to three times per day. Symptomatic treatments were used for hyperuricaemia, hyperkalaemia, hyperphosphataemia, hypocalcaemia, metabolic acidosis, and other metabolic disorders.

Daytime CVVH treatment

In all patients with TLS, vascular access was established by inserting an indwelling, double-lumen catheter into the femoral vein. The Prismaflex® CRRT system (Gambro Lundia AB, Lund, Sweden) with the M60 or M100 filter was adopted with the CVVH treatment mode. Replacement fluids were based on the modified Port carbonate formula and serum potassium concentrations of the patients to adjust the potassium concentration in the replacement fluid. In this study, 80% pre-dilution and 20% post-dilution were used to prepare the replacement fluid. We used a replacement fluid flow of 30 to 50 mL/kg·h, a blood flow of 3 to 5 mL/kg·min, and the amount of ultrafiltration was set according to the condition of the disease. For anticoagulation, 100 mg heparin was added to 1000 mL normal saline, which was used to presoak the blood filters and catheters for 30 minutes, followed by rinsing with 1000 mL normal saline. The first dose of low-molecular-weight heparin was 50 to 80 IU/kg using 5 to 10 IU/kg·h unfractionated heparin or 1 to 2 IU/kg·h low-molecular-weight heparin calcium to maintain anticoagulation. Patients with TLS were treated at the bedside for 8 to 12 hours during the daytime based on their condition. Heparin-free dialysis was administered to patients with severe coagulation abnormalities. Arterial blood flow was blocked once every 30 minutes, and 100 to 200 mL normal saline was used to flush the pipeline and the filter. When the pipeline had a blood clot or a transmembrane pressure >200 mmHg, CVVH was interrupted to allow the catheters and filters to be replaced before continuing treatment. Daytime CVVH continued until there was adequate recovery of renal function and urine output.

Data collection

Clinical and laboratory data were retrieved from the hospital's electronic medical records. During daytime CVVH treatment, vital signs, including temperature, heart rate, respiration, and mean arterial pressure, were recorded every 30 minutes. Urine output and clinical symptoms were also monitored. Serum creatinine, electrolytes, and uric acid levels were measured before and after treatment. The incidence of complications was also closely monitored to evaluate the safety of the treatment. All of the patients with TLS underwent follow-up for 6 months to assess their prognosis.

Results

Patients' demographics

Eight patients with TLS were identified in this study (boys = 7; girls = 1; age range, 5–14 years) (Table 1). There were five newly treated cases of acute lymphoblastic leukaemia and three newly treated cases of

Table 1. Main clinical features of the eight children with tumour lysis syndrome.

Patient number	Sex	Age (y)	Tumour type	Initial laboratory findings						Time between chemotherapy and the first haemopurification (d)	Total duration of daytime CVVH (h)	Treatment efficacy	Prognosis
				Urine output (mL)	Serum creatinine (μmol/L)	Serum phosphate (mmol/L)	Serum potassium (mmol/L)	Serum uric acid (mmol/L)	Serum total calcium (mmol/L)				
1	Male	10	ALL	20	135	4.5	6.0	975	1.7	2	24	Effective	Alive
2	Male	12	ALL	2700	181	4.2	5.6	420	1.2	2	80	Effective	Alive
3	Male	14	ALL	1800	130	4.4	4.6	255	1.4	3	14	Effective	Alive
4	Male	6	ALL	1470	225	4.8	3.9	2342	0.8	3	23	Effective	Alive
5	Male	11	NHL	80	190	4.2	3.6	349	1.7	3	24	Effective	Alive
6	Female	12	NHL	180	187	4.0	4.7	2800	1.3	3	22	Effective	Alive
7	Male	9	ALL	2600	107	3.8	6.5	450	1.3	3	8	Effective	Alive
8	Male	5	BL	807	137	4.2	6.2	1057	1.4	2	40	Effective	Alive

CVVH, continuous veno-venous haemofiltration; ALL, acute lymphoblastic leukaemia; NHL, non-Hodgkin lymphoma; BL, Burkitt's lymphoma.

lymphoma. All of the patients had varying degrees of nausea. There were two cases of enuresis, one case of oliguria, two cases of shortness of breath, one case of oedema, and one case of fever. According to the diagnostic criteria of the Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guidelines for Acute Kidney Injury (AKI) published in 2012,[19] all (n = 8) of the patients with TLS had AKI. Four patients had Stage 2 AKI and four had Stage 3 AKI. All of the patients had hyperphosphataemia, four had hyperkalaemia, four had hyperuricaemia, and two had hypocalcaemia.

Efficacy of daytime CVVH

All of the patients with TLS received one to 10 CVVH treatments (with a total treatment duration of 8–80 hours) (Figure 1). Urine output, uric acid, potassium, phosphate, and calcium levels all returned to normal levels, but recovery of renal function was relatively slow. Urine output in the three patients with anuria or oliguria returned to normal 3 days after CVVH. Six patients still had a continuous increase in serum creatinine levels, but two patients showed a decline in serum creatinine levels 5 days after CVVH. Thirteen days after CVVH treatment, serum creatinine levels returned to normal in three patients and greatly declined in three others. Serum creatinine levels remained high in two patients at this time. Serum creatinine levels had returned to normal in all of the patients 23 days after CVVH. Normal phosphate levels were restored in all eight patients with hyperphosphataemia 5 days after CVVH. Potassium levels returned to normal 1 day after CVVH in the three patients with hyperkalaemia. One patient with hyperkalaemia showed normal potassium levels 8 days after CVVH. Of the four patients with hyperuricaemia, uric acid levels returned to normal 4 days after

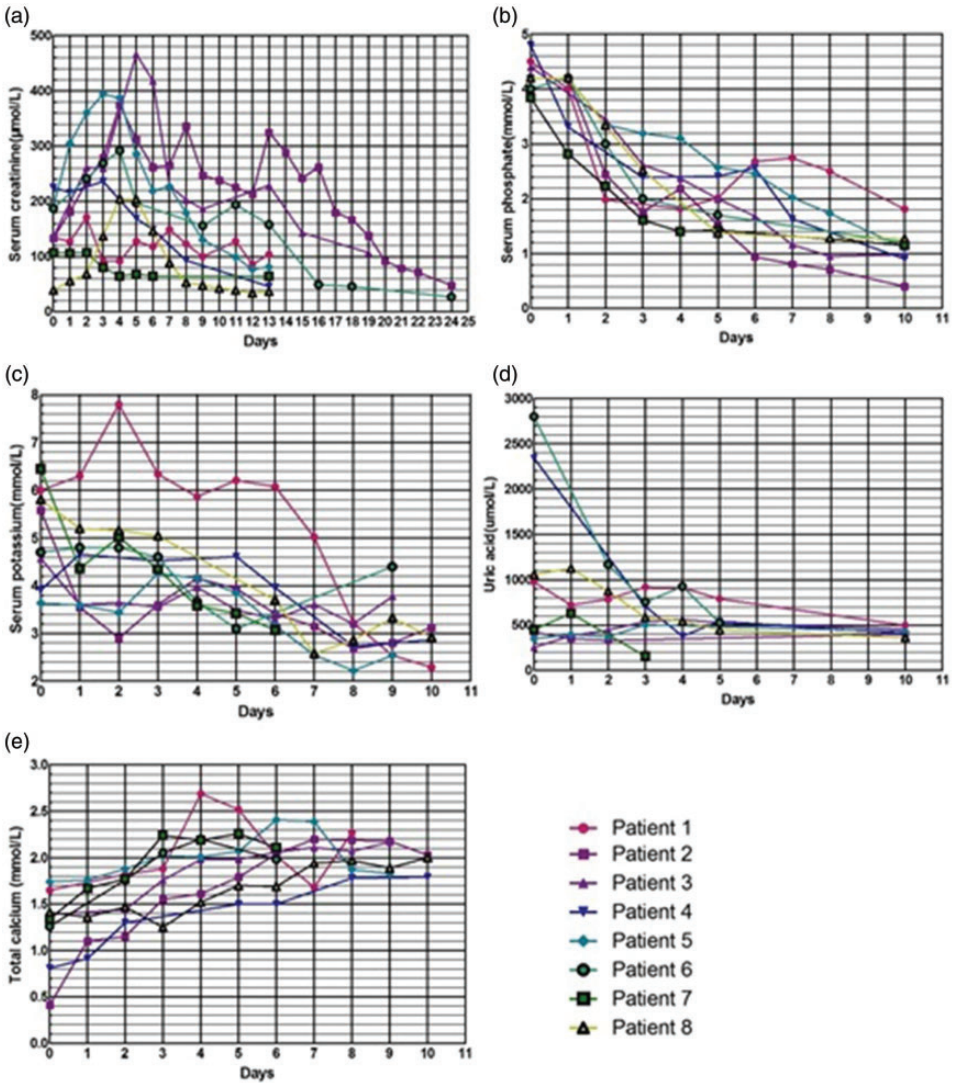

Figure 1. Laboratory findings during daytime continuous veno-venous haemofiltration. Time 0 represents the time at which daytime continuous veno-venous haemofiltration was initiated.

CVVH in three patients and after 10 days in the remaining patient. Two patients with hypocalcaemia recovered 2 days after CVVH.

Adverse reactions

None of the patients experienced bleeding, hypotension, thrombosis, allergies, or other complications after daytime CVVH treatment.

Follow-up and prognosis

All eight patients with TLS recovered and were discharged from the hospital. The duration of stay at the hospital ranged from 1 week to 25 days. As of the

6-month follow-up, one patient (case number 2) had died from pneumonia caused by *Stenotrophomonas maltophilia* during a second round of chemotherapy. The remaining seven patients survived with normal renal function.

Discussion

To the best of our knowledge, this is the first report of daytime CVVH in paediatric patients with TLS. In our study, all of the children completely recovered. This finding indicates the effectiveness of daytime CVVH for managing children who are critically ill due to TLS.

Although CRRT has beneficial effects in patients with TLS, the timing of the initiation of CRRT is still debatable. Despite optimal care, severe AKI develops in some patients and requires renal replacement therapy. Previous studies have demonstrated that AKI and dialysis requirements are strong predictors of a poor outcome in TLS.[20] The indications for dialysis are hyperkalaemia >6 mEq/L, serum creatinine levels >10 mEq/L, hyperphosphataemia >10 mEq/L, serum uric acid levels >10 mEq/L, symptomatic hypocalcaemia, fluid overload, severe acidosis, and uremia.[6,21] The 2012 KDIGO Clinical Practice Guideline for AKI states that patients should receive CRRT as soon as possible based on not only their blood urea nitrogen and creatinine levels, but also on their underlying disease, volume overload, degree of impairment of other organs, metabolite load, nutritional support, and volume of liquid input.[19] The indications for renal replacement therapy in patients with TLS are similar to those in patients with AKI attributable to other causes.[22] However, lower thresholds may be considered in the setting of TLS because of potentially high rates of potassium release and accumulation, particularly in patients with oliguria.[2] In patients with TLS, hyperphosphataemia-induced symptomatic hypocalcaemia may also warrant dialysis.[2] Recent studies have also shown that CRRT may be an effective therapeutic modality for patients with TLS, not only as renal replacement therapy, but also as a cytokine modulator.[19] In our study, all of the patients recovered from AKI, which suggested that early initiation of CVVH might improve outcomes of TLS. Because of the complex nature of TLS and the ongoing controversy regarding early versus late initiation of CVVH therapy in critical situations, developing more clinical trials for definitive answers is still vital.

Classic continuous CVVH involves continuous 24-hour renal replacement therapy. Classic continuous CVVH requires continuous anticoagulation, which results in an increased risk of bleeding and the loss of haemoglobin and albumin. This is also a time-consuming, labour-intensive, expensive treatment. Adsorption is an important way by which CVVH removes cytokines.[23] This exogenous scavenging approach is affected by not only the mediators themselves, but also the sieve coefficient of the filter, the transmembrane pressure, the adsorption capacity of membrane, and the therapeutic volume. In CVVH, new filters have the strongest scavenging capacity for removing cytokines.[24] Therefore, levels of tumour necrosis factor-α, interleukin-6, and other inflammatory cytokines are significantly reduced after 6 hours of treatment. This scavenging rate significantly decreases after 8 hours of treatment, reaching almost zero after 12 hours. In 1998, Breen et al.[25] proposed an intermittent CVVH treatment approach to allow for reuse of the filter, as with a normal dialyzer, which would reduce the cost of treatment. The scavenging rate was improved by removing the membrane protein layer and adsorbents from the filter. The protocol used for daytime CVVH in their study was most similar to that reported by

Van Malderen et al.[26] Van Malderen et al.[26] described intermittent veno-venous haemodiafiltration for treating acute renal failure and reported good treatment outcomes. In the current study, the eight patients with TLS mainly received CVVH during the daytime. This allowed the patients to achieve sufficient rest at night and provide functional rehabilitation and time for restoration of immune balance under pathological conditions. In fact, we may regard daytime CVVH as a hybrid therapy. This therapeutic approach facilitated recovery of damaged organs and minimized labour consumption. Daytime CVVH had a minimal effect on plasma concentrations of vasoactive drugs, antibiotics, infused amino acids, lipid emulsion, and other nutrients. This therapy also reduced the loss of nutrients and drugs in the bloodstream, and required removal of more volume overload during the day. More importantly, daytime CVVH minimized the problem of blood clotting on the filter and prevented a low filtration efficiency caused by a saturated filter and microthromboembolism during the 24-hour CVVH treatment. The volume of replacement and ultrafiltration should be increased in hypercatabolic patients. Patients with poor control in azotaemia should proceed with 24-hour uninterrupted CVVH.

Our study has a limitation that should be noted. Because few patients with TLS required CVVH, we were unable to perform a randomized, controlled trial and compare outcomes with other renal replacement therapies.

In conclusion, daytime CVVH is an effective and promising treatment for patients with TLS. Because only eight patients were included in this study, a larger, multicentre, prospective study is required to determine the ideal time and dosage of daytime CVVH for treating paediatric TLS.

Ethics approval

The study was approved by the Ethical Review Board of Investigation in Human Beings of the West China Second University Hospital, Sichuan University.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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