CONTINUOUS ARTERIOVENOUS HEMODIAFILTRATION AND HEMOFILTRATION IN THE TREATMENT OF TUMOR LYSIS SYNDROME

(Received 15 January, 1992)

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SUMMARY

Acute tumor lysis syndrome and associated renal failure are frequently seen in children with B cell leukemia and lymphoma. In patients resistant to conservative management, renal replacement therapy is required. Continuous arteriovenous hemodiafiltration (CAVHD) and continuous arteriovenous hemofiltration (CAVH) were used successfully in the treatment of tumor lysis syndrome and renal failure preceding chemotherapy in a child with B cell leukemia. The advantages of the methods are discussed.

Key words: Continuous arteriovenous hemofiltration, continuous arteriovenous hemodiafiltration, B cell leukemia, B cell lymphoma, tumor lysis syndrome.

INTRODUCTION

The metabolic abnormalities known collectively as the "acute tumor lysis syndrome" consist of hyperuricemia, hyperkalemia, hyperphosphatemia and the resultant hypocalcemia, which are associated with the massive destruction of neoplastic cells (1,2). These are particularly severe in children with advanced stage Burkitt lymphoma and B cell acute lymphoblastic leukemia (ALL) as a consequence of rapid tumor cell proliferation, large tumor burden at presentation and a very rapid response to chemotherapy (2,3). Patients are routinely treated with vigorous intravenous fluid hydration, alkalinisation of the urine and allopurinol in an effort to prevent tumor lysis syndrome and renal failure (4,5). Acute renal failure, nevertheless, may develop and becomes life threatening.

Continuous arteriovenous hemofiltration (CAVH) and continuous arteriovenous hemodiafiltration (CAVHD) have been reported to be safe and effective in the treatment of acute renal failure in critically ill adults (6-8) and children (9,10). We report our experience with CAVH and CAVHD in the management of acute tumor lysis syndrome and renal failure seen before treatment in a child with B cell ALL.

METHODS

A Hemospal AN 69-S hemofilter with a surface area of 0.5 m2 was used. The filter, including the arterial and venous connections, had an internal volume of 100 ml and was primed with two liters of heparinised (5000 IU/1) saline. Two 10 Fr Hemoacces catheters were inserted into the artery and vein using the Seldinger technique. After an initial heparinisation with 15 IU/kg, the arterial and venous lines were connected to the hemofilter.

CAVHD, with which the solute clearance is higher, was used during the first 20 hours (Fig. 1). Peritoneal dialysate fluid with potassium added as required was infused through the filter in the opposite direction to blood flow at a rate of 1000 ml/hr. The ultrafiltration rate was approximately 500 ml/hr and balance was maintained through the replacement of the ultrafiltrate with

electrolyte solutions. Heparinisation was done by infusion into the arterial line at an average rate of 5 IU/kg/hr and followed with the activated clotting time. A schema of the CAVH system is shown in Fig. 2. After infusion of dialysate fluid through the filter was stopped, ultrafiltration of blood and replacement of the ultrafiltrate by balanced electrolyte solutions were continued during CAVH. The same filter was used for CAVHD and CAVH for a total of 90 hours.

Chemotherapy was administered according to a modified B cell neoplasia, BFM-90 protocol, starting with a five day "Vorphase" consisting of prednisolone 30 mg/m2/day P.O. and cyclophosphamide 200 mg/m2/day i.v. Nutrition was provided orally.

RESULTS

A 12 year-old boy, body weight 35 kg, presented with a 10 day history of weakness, pallor, abdominal pain, vomiting and purpuric skin lesions. The liver was palpated 6 cm and the spleen was palpated 3 cm below the costal margins. He also had gross hematuria. In the peripheral blood count, hemoglobin was 5.4 g/dl, hematocrite 0.18 l/l, leukocytes 25.0×10^9/l and platelets 30.000/mm3. Leukocyte differential count revealed 59% and bone marrow examination revealed 86% lymphoblasts showing FAB-L3 morphology. The blasts were found to be surface immunoglobulin (IgM) positive, and B cell ALL was diagnosed.

Laboratory evaluation revealed a raised lactate dehydrogenase of 4500 U/l, uric acid of 21.5 mg/dl, urea of 303 mg/dl and creatinine of 6.7 mg/dl. The serum sodium level was 128 mEq/l, potassium level was 6.6 mEq/l and calcium level was 5.2 mg/dl. Urine output was diminished, though not oliguric.

To increase diuresis and to combat with the metabolic derangements due to acute tumor lysis syndrome and associated renal failure, treatment was started with intravenous fluids at 3000 ml/m2/24 hr, bicarbonate 40 mEq/l, dopamine 5 µg/kg/min, furosemide and allopurinol. The patient was also supported with red blood cell and platelet transfusions. Although the urine flow was maintained above 2 ml/kg/hr, laboratory values at the 36th hour were uric acid 25.4 mg/dl, urea 261 mg/dl, creatinine 6.3 mg/dl, sodium 124 mEq/l, potassium 3.3 mEq/l and calcium 6.2 mg/dl; somnolance ensued. Since hemodialysis facilities could not be accessed, it was decided to institute renal replacement therapy with CAVHD.

CAVHD was started using the left femoral artery and vein. The biochemical changes are shown in Fig. 3. A clear state of consciousness was achieved by the fourth hour and uric acid decreased to 11 mg/dl, urea to 43 mg/dl and creatinine to 2.1 mg/dl by the 10th hour. Under CAVHD, cytotoxic chemotherapy with prednisolone and cyclophosphamide was started. With maintenance of the metabolic balance even after initiation of chemotherapy, CAVHD was discontinued at the 20th hour and CAVH, with which the solute clearance is less, was performed with the same filter until the 90th hour. The patient responded well to chemotherapy, and remission was achieved after the first intensive block following "Vorphase". Renal function has remained normal.

DISCUSSION

The tumor lysis syndrome is a direct result of the degradation of malignant cells with release of uric acid, phosphorous and potassium (1-5). Precipitation of calcium phosphate leads to hypocalcemia. Acute uric acid nephropathy is the most widely recognized cause of acute renal failure in patients with leukemia and lymphoma. Besides uric acid, precipitation of phosphates and xanthine add to the renal injury. Since these metabolites are mainly excreted by the kidney, a high urine flow is mandatory before treatment is initiated (2,11). Although seen frequently following chemotherapy, renal failure in patients with B cell leukemia and lymphoma may precede chemotherapy as a result of spontaneous tumor cell lysis, infiltration of the kidneys or tumor compression (3,5,12).

The factors associated with an increased risk of renal failure have been defined as large tumor burden, elevated LDH and uric acid levels and inadequate urine output (2,3). In patients with metabolic problems resistant to conservative management, renal replacement therapy is required before or during induction chemotherapy (4,5). Conventional hemodialysis and peritoneal dialysis are the methods classically used.

Described by Kramer et al. in 1977, CAVH is a continuous extracorporeal process by which fluid, electrolytes and solutes smaller than 10,000 daltons are ultrafiltrated from the blood through semipermeable fibers or membranes by convection, simulating glomerular filtration (6). Flow of blood through the system is driven by the patient's systemic arterial blood pressure; no blood pump is used. The method was introduced first to remove excess fluid and later in the treatment of critically ill patients with multiorgan system dysfunction and renal failure (7,8). Although fluid overload is controlled efficiently by CAVH, the procedure is limited in solute removal with a creatinine clearance of approximately 10-15 ml/min (13). By infusing dialysate fluid through the ultrafiltrate compartment of the filter, the technique of CAVHD has been developed(14). The dialysate flow rate (15-30 ml/min) is considerably slower than blood flow (50-150 ml/min), allowing equilibration between plasma and dialysate within the filter (15). Solute removal is thus greatly improved up to four times (15,16).

Both methods have been reported to be safe and effective in children, including neonates (9,10).

CAVHD before and during the initial 10 hours of chemotherapy and CAVH until the 90th hour proved to be effective in the correction of the metabolic derangements and allowed early institution of chemotherapy in our patient. Fluid and electrolyte balance was easily maintained and a dramatic improvement in the general condition of the patient and metabolic control were achieved within hours after initiation of the procedure. Improvement continued even after starting chemotherapy.

Although hemodialysis and peritoneal dialysis are still the standard methods of treatment in acute renal failure, CAVH and CAVHD have apparent advantages under certain conditions (8,-10,15). Hemodialysis has the disadvantages of osmotic and hemodynamic instability, necessity of repeating the procedure when the production of endogenous toxins is continuing and the re quirement of expensive mechanical apparatus and specially trained personnel. Peritoneal dialysis is simpler, is associated with greater cardiovascular stability and is more efficient at fluid removal but less efficient at the removal of waste products. Peritoneal dialysis entails the risks and complications of catheter placement, can lead to respiratory compromise, is associated with a high incidence of infection in critically ill patients and may be contraindicated because of intraabdominal disease, surgery or coagulopathy. CAVH and CAVHD, however, are simple, provide metabolic and cardiovascular stability, permit administration of parenteral nutrition, can be managed in intensive care units without the use of expensive equipment and obviates the need to transfer the patient from one center to another for dialysis.

Besides being an important alternative to standard hemodialysis and peritoneal dialysis in critically ill patients with renal failure, CAVH and CAVHD might be the methods of choice in children with acute tumor lysis and renal failure (10,17). Patients with B cell malignancies frequently have extensive abdominal disease, abdominal surgery and bleeding tendencies, which may be contraindications to peritoneal dialysis. Because of the continuing cytolysis, metabolic stability can be maintained more easily, making administration of chemotherapy and nutrients possible and precluding large swings which can be seen between treatments with hemodialysis. Although the most important factors which determine the delivery of drugs to the filter such as the degree of protein binding are well known, data on the clearance of specific chemotherapeutic drugs by CAVH and CAVHD are unfortunately not yet available (13). The procedure can be easily applied in the same center where the staff is experienced in administering chemotherapy. Being safe and effective, it is suited well to the prevention and treatment of renal failure associated with tumor lysis.

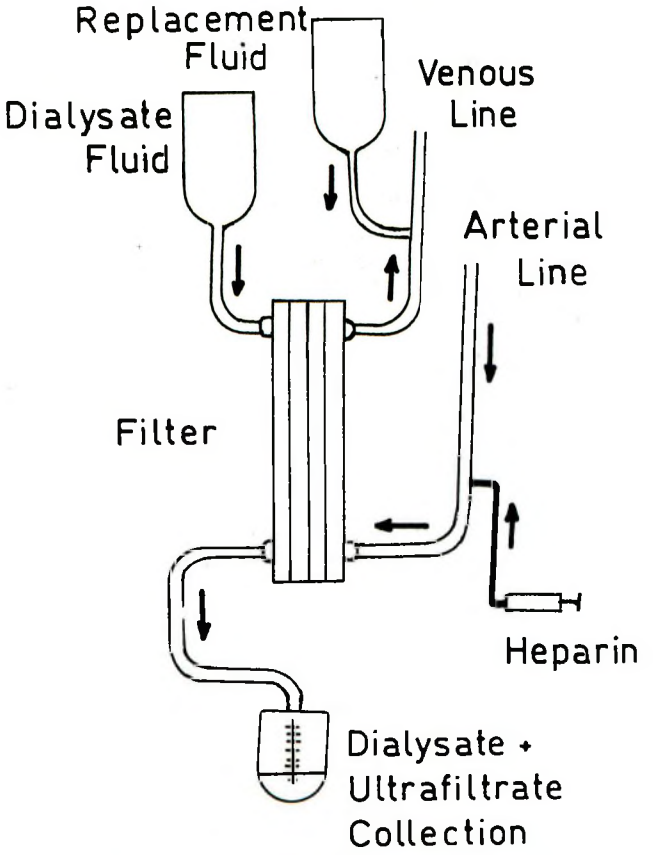

Fig 1: Schematic illustration of continuous arteriovenous hemodialfiltration.

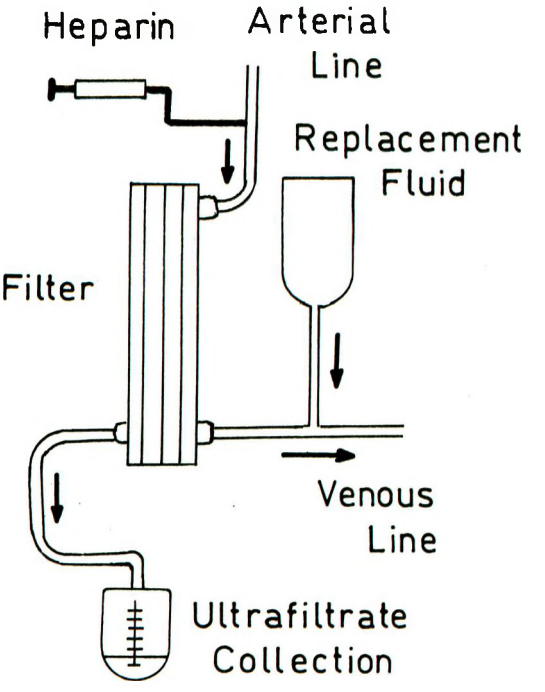

Fig 2: Schematic illustration of continuous arteriovenous hemofiltration.

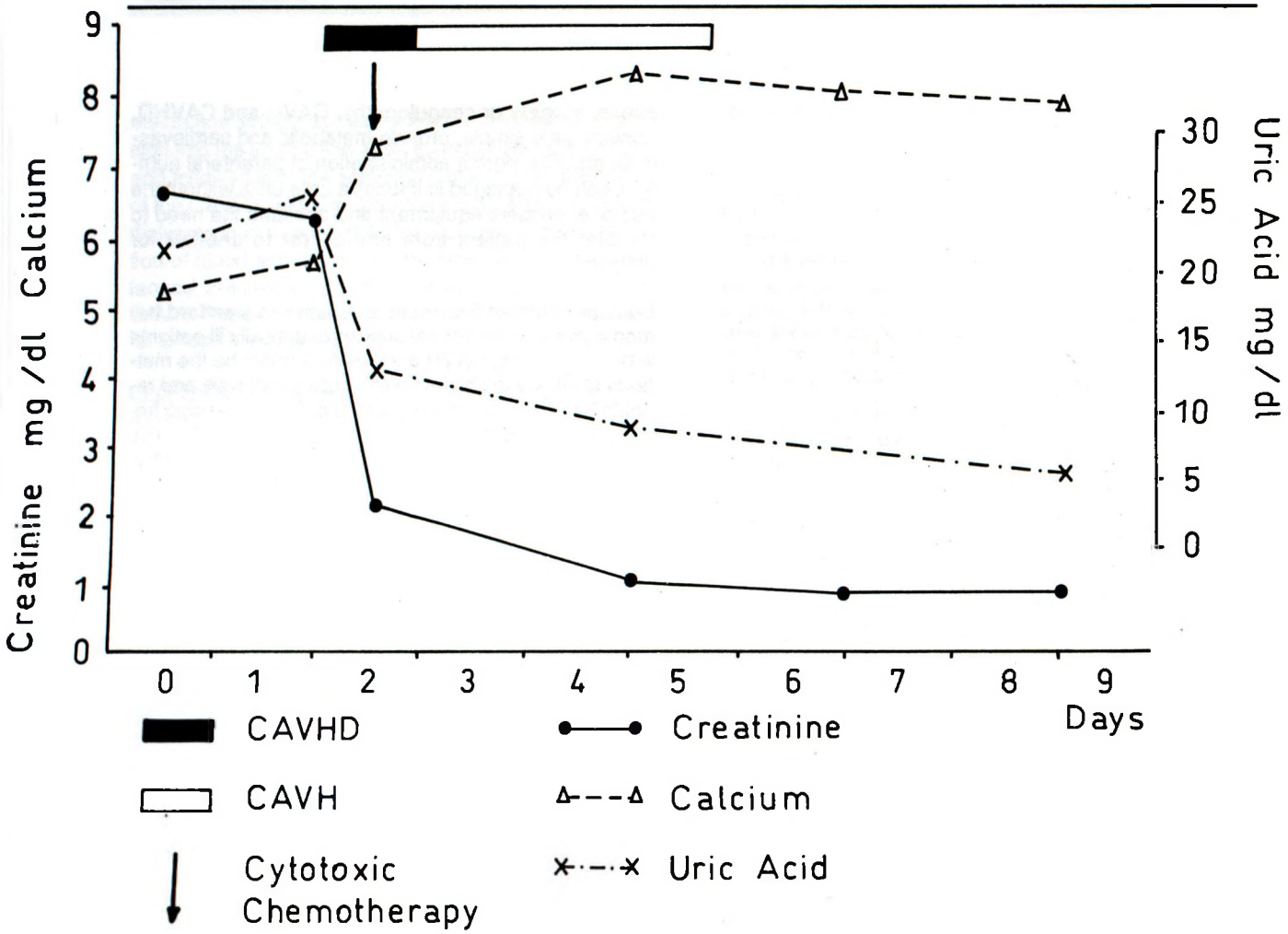

Fig. 3. Changes in serum creatinine, calcium and uric acid.

REFERENCES

1. Cadman EC, Lundberg WB, Bertino JR. Hyperphosphatemia and hypocalcemia accompanying rapid cell lysis in a patient with Burkitt's lymphoma and Burkitt cell leukemia. Am J Med 1977; 62:283-290.
2. Cohen LF, Balow JE, Magrath IT, Poplack DG, Ziegler JL. Acute tumor lysis syndrome: a review of 37 patients with Burkitt's lymphoma. Am J Med 1980; 68:486-491.
3. Stapleton FB, Strother DR, Roy S, Wyatt RJ, McKay CP, Murphy SB. Acute renal failure at onset of therapy for advanced stage Burkitt lymphoma and B cell acute lymphoblastic leukemia. Pediatrics 1988; 82:863-869.
4. Lange B, D'Angio G, Ross AJ, O'Neill JA, Packer RJ. Oncologic emergencies. In: Pizzo PA, Poplack DG, eds. Principles and practice of pediatric oncology. Philadelphia: J.B. Lippincott, 1989; 799-822.
5. Hutter JJ. Principles of total care: physiologic support. In: Fernbach DJ, Vietti TJ, eds. Clinical pediatric oncology. 4th ed. St. Louis: Mosby Year Book, 1991;231-248.
6. Kramer P, Wigger R, Rieger J, Mathael D, Scheler F. Arteriovenous hemofiltration: a new method for treatment of overhydrated patients resistant to diuretics. Klin Wochenschr 1977;55:1121-1122.
7. Lauer A, Saccaggi A, Ronco C, Belledonne M, Glabman S, Bosch JP. Continuous arteriovenous hemofiltration in the critically ill patient. Ann Intern Med 1983; 99:455-460.
8. Kaplan AA, Longnecker RE, Folkert VW. Continuous arteriovenous hemofiltration: a report of six months' experience. Ann Intern Med 1984; 100:358-367.
9. Lieberman KV, Nardi L, Bosch JP. Treatment of acute renal failure in an infant using continuous arteriovenous hemofiltration. J Pediatr 1985; 106:646-649.
10. Bishof NA, Welch TR, Strife F, Ryckman FC. Continuous hemodiafiltration in children. Pediatrics 1990; 85:819-823.
11. Tsokos GC, Balow JE, Spiegel RJ, Magrath IT. Renal and metabolic complications of undifferentiated and lymphoblastic lymphomas. Medicine 1981; 60: 218-229.
12. Glicklich D, Sung MW, Frey M. Renal failure due to lymphomatous infiltration of the kidneys: report of three new cases and review of the literature. Cancer 1986; 58:748-753.
13. Bickley SK. Drug dosing during continuous arteriovenous hemofiltration. Clin Pharm 1988; 7:198-206.
14. Geronemus R, Schneider N. Continuous arteriovenous hemodialysis: a new modality for the treatment of acute renal failure. Trans Am Soc Artif Intern Organs 1984; 30:610-613.
15. Dickson DM, Hillman KM. Continuous renal replacement in the critically ill. Anaesth Intens Care 1990; 18:76-92.
16. Maher ER, Hart L, Levey D et al. Comparison of continuous arteriovenous haemofiltration and haemodialysis in acute renal failure. Lancet 1988; 1:129.
17. Heney D, Essex-Cater A, Brocklebank JT, Bailey CC, Lewis IJ. Continuous arteriovenous haemofiltration in the treatment of tumor lysis syndrome. Pediatr Nephrol 1990; 4:245-247.