



### Continuous Venovenous Hemodiafiltration in Three Newborn Patients with Hyperammonemia

Hiperamonemili Üç Yenidoğan Bebekte Devamlı Venovenöz Hemodiafiltrasyon

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#### ABSTRACT

In newborns, hyperammonemia leads to encephalopathy which is usually characterized by vomiting, hypotonia, lethargy, seizures and coma. Continuous venovenous hemodiafiltration (CVVHDF) is a modality choice to treat acute decompensation in hyperammonemia. Here we report three newborn patients with hypotonia, convulsion and hyperammonemia. In the first three days of life, their serum ammonia levels were 4609, 1023 and 1949 µg/ml. They were successfully treated with CVVHDF and serum ammonia levels subsequently decreased to 268, 164 and 65 µg/ml in the first 24 hours of treatment. The complications were mild hypothermia and anemia.

**Key words:** Hemodiafiltration, Neonate, Hyperammonemia.

#### ÖZET

Yenidoğan bebeklerde hiperamonemi, hipotoni, letarji, nöbetler ve koma ile karakterize ensefalopati tablosuna yol açabilir. Akut dekompanse olmuş hiperamonemi tedavisinde devamlı venovenöz hemodiafiltrasyon tedavi seçeneği olabilir. Burada hipotoni, konvülsiyon ve hiperamonemi olan üç yenidoğan olgusu sunulmuştur. Yaşamlarının ilk üç gününde amonyak değerleri 4609, 1023, 1949 microgram/ml idi. Devamlı venovenöz hemodiafiltrasyon ile başarılı bir şekilde tedavi edilerek tedavinin ilk 24 saatinde amonyak değerleri 268, 164 65 microgram/ml'ye azaltıldı. hafif hipotermi ve anemi komplikasyon olarak saptandı.

**Anahtar kelimeler:** Hemodiafiltrasyon, Yenidoğan, Hiperamonemi.

#### INTRODUCTION

Hyperammonemia due to the metabolic diseases mostly develop in the early newborn period and deteriorates the newborn's condition rapidly. Ammonia levels exceeding 400-500 µmol/L with significant clinical findings require prompt intervention.

Different dialysis modalities, such as continuous hemofiltration, intermittent hemodialysis

(HD), continuous hemodialysis and continuous hemodiafiltration (CHDF) are the most effective treatment methods for decreasing serum ammonia levels<sup>1-10</sup>. Continuous venovenous hemodiafiltration (CVVHDF) is a modality choice to treat acute decompensation in inborn error of metabolism. In CVVHDF, transport is achieved with both convective and diffusive techniques, there is less hemodynamic instability during ultrafiltration due to isotonic fluid removal from the

patient. Despite these advantages, problems such as difficulty of blood access, large priming volume and hypothermia were reported<sup>11</sup>.

Here we report three patients with hyperammonaemia, successfully treated with CVVHDF.

## CASES

In all three patients, a 7 F dual-lumen catheter was inserted to right atrium via subclavian vein and a bedside system CVVHDF (Prisma M-10, Gambro Healthcare, Lakewood, CO) was started. A dialyzer-filter (Prisma M-10) which required 48 ml as blood the priming volume, and a special circuit with warmer coil were used. During the procedure, membrane change was not needed in any of the cases. Hollow fiber material of M10 was AN69 (Acrylonitrile and sodium methallyl sulfonate copolymer), effective surface area was 0.042 m<sup>2</sup> and total volume of blood circuit including hemofilter/dialyzer was 50 ml ± 10%. M60 type membrane was not used as the priming volume was high for the neonates. Multibic 0-2-4 fluids were used as replacement fluid according to the patient's serum potassium levels. In order to maintain the activated clotting time between 170 and 210 seconds, heparine (0-20 IU/kg/h) was administered according to patient's coagulation status. The blood flow rate of CVVHDF was 8-10 ml/kg/min, dialysate flow rate was 2000 cc/1.73m<sup>2</sup>/h, the hemofiltration rate was 2000 cc/1.73m<sup>2</sup>/h and total hemodiafiltration rate was 4000 cc/1.73 m<sup>2</sup>/h. The patients were monitored and observed in the incubator. None of the cases experienced any catheter complication and catheters were removed 72 hours after discontinuation of CVVHDF.

### CASE 1.

The patient was a female infant of healthy parents, with I ° consanguinity. She had a healthy sister. She was born in 39 weeks of gestational age. Apgar scores were 8 and 9 at 1<sup>st</sup> and 5<sup>th</sup> minutes of life. Body weight was 3000 g, length

was 48 cm. She was breastfed. On the 3<sup>rd</sup> day, she was admitted to hospital for hypotonia and transferred to NICU for metabolic acidosis and early neonatal sepsis. At admission, she was 2660 g, lethargic, tachycardic (193/min) and tachypneic (65/min). She was dehydrated. Auscultatory findings of the heart and lungs were normal. She had no hepatosplenomegaly. Newborn reflexes were nonreactive.

Laboratory findings showed: Hb: 19 g/dl, WBC: 21.200/mm<sup>3</sup> (20% banded neutrophiles, 52% segmented neutrophiles), PCT: 1.35 pg/ml, blood gas values: pH: 7.32, pCO<sub>2</sub>: 23 mm Hg, BE: -16.3mEq/l, HCO<sub>3</sub>: 8.6mEq/l. BUN, creatinine, electrolytes were in normal limits, blood glucose was 95 mg/dl, acetone was positive. Serum ammonia level was 4609 µg/ml, serum lactate 42.1 mg LA/dl and serum pyruvate 1.5 mg PA/dl. Cranial ultrasonography was normal.

She was intubated and mechanically ventilated. As she had 340 g weight loss, 20 cc/kg NaCl was infused and ampicillin, cefotaxime, carginic acid, sodium benzoate, carnitine and thiamine were introduced immediately. Adequate caloric intake (120 kcal/kg/day) was supplied as parenteral glucose. A central venous 7-F catheter was applied in subclavian vein and CVVHDF was initiated in 3 hours of admission. Metabolic acidosis ameliorated after 4 hours of CVVHDF. Serum ammonia level decreased to 789 µg/ml after 16 hours and decreased to 268 µg/ml after 24 hours (Figure 1) and CVVHDF was stopped. During hemodiafiltration, infant had anemia (Htc: 26%), mild hypothermia (35.9 °C) for one hour and prolonged PT and PTT. Erythrocyte and fresh frozen plasma was transfused. Her level of consciousness improved. She was fed on the 6<sup>th</sup> day of admission with 1 g/kg of amino acid, antibiotics were stopped after 10 days. She had normal values of serum ammonia in the following days and sodium benzoate and carginic acid were stopped and she was discharged on 24<sup>th</sup> day of life. Tandem mass and urinary organic acid tests

showed normal values. She is now 13 months old, she is well and still observed in outpatient clinic.

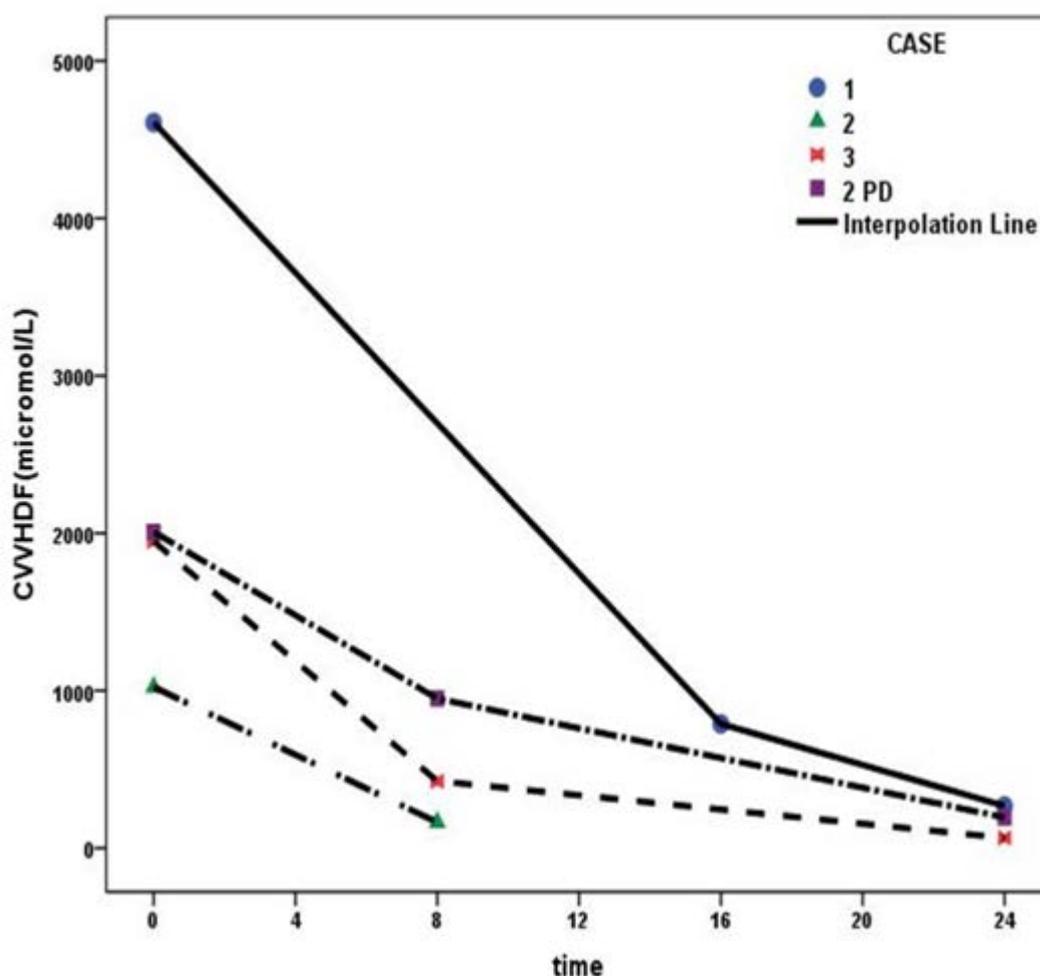
### CASE 2.

The patient was a male infant born after caesarean section to a diabetic mother, P2/G1. There was no consanguinity. He was 35 weeks old and his birth weight was 5000 g (>90%), height 55 cm (>90%). He had hypoglycemia in the first hour of life, umbilical venous catheter was inserted and high glucose infusion (16 mg/kg/min) was administered. On the second day, he had hyperthermia, ampicillin and netilmycin were initiated. On the third day of life, he was hypotonic, he had convulsion and was intubated and mechanically ventilated. Blood gases were normal, serum keton was negative and serum ammonia level was 500  $\mu\text{g/ml}$ . Na benzoate (130 mg/kg) was started. Control serum ammonia level was 2008  $\mu\text{g/ml}$ . As CVVHDF was not available at the moment, peritoneal dialysis was initiated. Eight hours later, serum ammonia level decreased to 950  $\mu\text{g/ml}$  and 24 hours later 195  $\mu\text{g/ml}$  (Figure 1) and dialysis was stopped in the 2<sup>nd</sup> day of treatment. In the 6<sup>th</sup> day, he was extubated, 1 g/kg/day aminoacid and 2 g/kg/day lipid, B vitamin complex and carnitine were started and on the 11<sup>th</sup> day, aminoacid concentration was increased to 1.5 g/kg/day. Plasma quantitative aminoacid levels and urine orotic acid levels were compatible with carbamoyl phosphate synthetase deficiency. Differential diagnosis with ornithine transcarbamylase deficiency was made due to increased serum glutamine and alanine levels with normal urine orotic acid levels. On the 17<sup>th</sup> day, a low protein diet special formula and arginine were started, he could be fed full enterally on the 26<sup>th</sup> day. On the 27<sup>th</sup> day, the clinical course was complicated and characterized by severe vomiting

and hypotonia. Serum ammonia level increased to 1023  $\mu\text{g/ml}$ . A subclavian venous catheter (7F) was inserted and CVVHDF was started. In 8 hours, ammonia level decreased to 164  $\mu\text{g/ml}$  (Figure 1). Hematocrite level decreased (from 30% to 24%), he had no hypothermia. CVVHDF was stopped. His level of consciousness improved. On the 34<sup>th</sup> day, serum arginine level was low and arginine was started. He was discharged on the 62<sup>nd</sup> day of life and now 16 months old. He is followed in the outpatient clinic and he has motor deficits.

### CASE 3.

A 3700 g male infant was born by caesarean section at 40 weeks as the first baby of a healthy non-consanguineous couple. He has been admitted to newborn unit for meningomyelocele. Ampicillin and netilmycin were started. On the 2<sup>nd</sup> day, he began feeding and on the 4<sup>th</sup> day, he developed recurrent vomiting, hypotonia and convulsions. Feeding was stopped, infant was intubated and mechanically ventilated, phenobarbital and then phenytoin were infused for convulsions. Laboratory evaluation revealed: hb: 10.6 g/dl, wbc: 19500/mm<sup>3</sup>, platelet: 373000/mm<sup>3</sup>, blood smear: 60% segmented neutrophiles, %40 lymphocyte. Blood gas values, electrolytes, calcium, phosphor and glucose levels were normal. Serum ammonia level was 1949  $\mu\text{g/ml}$ . A central venous catheter was inserted, whole blood was used as the priming volume and CVVHDF was started. Serum ammonia level decreased to 426  $\mu\text{g/ml}$  after 8 hours and 65  $\mu\text{g/ml}$  after 24 hours (Figure 1). He had moderate hypothermia (35°C) during hemodiafiltration. His level of consciousness never improved. He died on the 7<sup>th</sup> day of life due to septic shock. Tandem mass test revealed non specific findings.



**Figure 1.** Ammonium levels of patients during continuous venovenous hemodiafiltration (CVVHDF) for patients and during peritoneal dialysis (PD) only for case 2.

## DISCUSSION

In these case reports we described the effectiveness of CVVHDF in three infants with neonatal onset hyperammonemia. Acute hyperammonemia is a medical emergency as excess ammonia may cause hyperammonemic coma. As ammonia has no osmolar effect, a rapid decline in ammonia levels does not cause any damage. Prompt therapy is mandatory to minimize the permanent brain damage<sup>12</sup> The emergency therapy includes dietary protein restriction with supplementation of high glucose intake to stop endogenous protein catabolism, and activation of

alternative nitrogen pathways by administration of sodium benzoate and/or phenylacetate. If the foregoing therapies fail to yield any appreciable change in the blood ammonia level within a few hours, hemodialysis or peritoneal dialysis should be used. Hemodialysis and HDF are more effective for reducing serum ammonia level as a result of higher dialysance<sup>1,2</sup> There are increasing reports about HDF use in the acute phase of hyperammonemia in infants<sup>3-7</sup> The advantage of continuous HDF over HD is that continuous HDF causes less hemodynamic instability during ultrafiltration. Furthermore, continuous HDF is

reported to be superior to HD and PD in the aspect of ammonia clearance, because the pore size of the filter is more suitable for removal of ammonia compared with that of HD. Unlike conventional intermittent hemodialysis, in which clearance may be achieved by diffusion down concentration gradients, clearance is most often dependent on convection or solute drag through ultrafiltration in continuous dialysis modalities. Such clearance is slower than the clearance achieved with conventional dialysis but is ultimately effective because the treatment is continuous rather than intermittent. However problems have been reported in neonates such as hypotension due to large priming blood volume, bleeding due to anticoagulation therapy, coagulation in the circuit, anemia and hypothermia<sup>8-10</sup>. In two of three patients, we reported hypothermia and anemia. It may be possible to overcome pediatric-specific problems by minimization of the priming volume, use of whole blood/erythrocyte as priming solution and temperature control of both the patient and the solutions in the circuit. As the first two patients had anemia, we used whole blood as the priming volume and had no anemia in the third patient.

As seen in Figure, CVVHDF was extremely effective to reduce ammonia levels in the present patients. However, peritoneal dialysis can also be performed for the same purpose. But, as it provides a slower clearance of ammonia; if it is possible, it is plausible to use extracorporeal dialysis if available in the unit. In the second case, as the patient had no central vascular access, we initially used peritoneal dialysis and had an effective, but slower decline in serum ammonia levels.

In conclusion continuous HDF should be considered as a treatment modality for symptomatic neonates with hyperammonemia to improve life-neurological prognosis of these diseases in the neonatal period. It is important to transfer patients with severe hyperammonemia as soon as possible to a specialized centre where HDF can be performed after initial pharmacological

therapy. However, peritoneal dialysis should not be delayed if vascular access is not in place or if HDF is not available.

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