The effectiveness of continuous venovenous hemofiltration in the treatment of acute crisis inborn errors of metabolism in children

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Summary

Objective: To evaluate of the effectiveness of continuous venovenous hemofiltration in the treatment of acute crisis of inborn errors of metabolism at National Children's Hospital. *Subject and method:* A prospective, intervention without the control group of 19 patients with an acute crisis of inborn errors of metabolism, who received continuous venovenous hemofiltration (CVVH) at the National Children's Hospital from January 2015 to December 2017. *Result:* 19 patients (male: 11, female: 8), ranging from 4 days to 6 years of ages met inclusion criteria. CVVH was indicated due to hyperammonemia (7/19) or severe metabolic acidosis (12/19). Prior to CVVH, pH was: 7.08 ± 0.2 and was normalized after 24 hours; NH_3 was 1052 ± 36µmol/l and decreased to normal range after 24 hours. 19/19 patients were comatose with responde to pain, in which 18/19 were alert. 1/19 patients died. Common complications were nosocomial infection (3/19) and hypokalaemia (2/19). *Conclusion:* CVVH was an effective treatment for children with an acute crisis of inborn errors of metabolism, reduced hyperammonemia after 24 hours and corrected pH after 36 hours with higher survival rate and less complication.

Keywords: Inborn errors of metabolism, acute crisis, CVVH.

1. Background

Inborn errors of metabolism (IEMs) are molecular genetic disorders caused by disorders of the genetic structure, leading to deficiency of enzymes, receptors, transport proteins, and co-factors. Causes of defects with varying levels of physical metabolism, the decompensated acute crisis is the most severe manifestation of IEMs that can cause death or severe neurological sequelae if not diagnosed early and treated promptly. The clinical presentation of acute decompensation syndrome was varied with non-specific symptoms: altered mental status (lethargy, coma), seizures or severe shock, and severe metabolic acidosis. Continuous venovenous hemofiltration is an emergency treatment that rapidly removes ammonia (NH3), metabolic toxins, and helps balance the metabolism of the body [1], [2]. Our study was done with the objective: *To evaluate the effectiveness of CVVH in treatment of acute crisis of inborn errors of metabolism at the National Children's Hospital of Vietnam.*

2. Subject and method

2.1. Subject

Nineteen patients were diagnosed with the acute crisis of IEMs and received CVVH at the National Children's Hospital of Vietnam from January 2015 to December 2017.

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2.2. Method

Study design: Prospective study, intervention without control group, before - after intervention.

Selection criteria: Patients diagnosed with IEMs with acute crisis and designated CVVH when: acute encephalopathy syndrome (lethargy, convulsion, coma), combining blood ammonia increased ≥ 400µmol/L or severe metabolic acidosis with pH < 7.2 [3].

Exclusion criteria: Deep coma (Glasgow Coma Score: 3 points), the patient's parents disagreed to participate and lack of information according to the research sample.

The process: Patients admitted to PICU and NICU were received conservative treatment with respiratory, circulatory and neurological support, nil per os, high glucose infusion at a rate of 8 - 10mg/kg/min, CVVH with PRISMA Flex System, Gambro's dialysis solution and filter, anticoagulation therapy as described in VNCH's CVVH protocol.

Treatment effectiveness was assessed through the following criteria:

Change of mental status, assessed with the Glasgow coma scale.

Effective ammonia reduction by continuous dialysis at T0 (before CVVH), T1 (after 6 hours), T2 (after 12 hours), T3 (after 24 hours) and T4 (after 36 hours).

Change of blood pH according to CVVH time as above.

Criteria for CVVH discontinuation: Blood levels of NH3 < 200µmol/L and/or no more acidosis.

CVVH time recorded in the number of days.

Adverse effects and complications: Bleeding, hypothermia, nosocomial infection…

Mortality and survival rate.

Statistical analysis: Statistical analysis was performed using SPSS (version 23.0 for Windows, IBM, North Castle, NY, USA). Statistical tests were used to compare the effectiveness of treatments in the 2 groups including: Chi-Square test, independent t-test, and paired t-test. The level of statistical significance was p-value less than 0.05.

3. Result

3.1. Characteristics of patients

In 19 patients with IEMs acute crisis, male: 11 patients (57.9%), female: 8 patients (42.1%). The mean age at the time of acute crisis was 10 ± 17 months, the smallest was 4 days old, the oldest was 72 months old. The average weight was 7.2 ± 4.2kg, the smallest was 3kg, the largest was 19kg.

Table 1. Distribution of patients with IEMs

IEMs	n	%
Organic acidemias	9	47.3
Ure cycle disorders (UCD)	4	21.2
Maple syrup urine disease (MSUD)	3	15.7
Beta ketothiolase deficiency (BKD)	2	10.5
Ketosis	1	5.3
Total	***19***	***100***

Comment: Organic acidemias for the highest proportion (47.3%), UCDs (21.2%), MSUD (15.7%), BKD (10.5%), and ketosis (5.3%).

3.2. The effectiveness of continuous venoveous hemofiltration in the treatment of acute crisis of IEMs

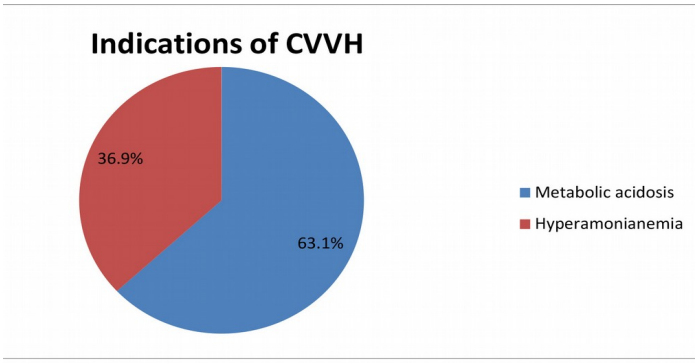

Figure 1. Indications of CVVH

Comment: Indications of CVVH: Metabolic acidosis 12/19 (63.1%), hyperammonemia 7/12 (36.9%).

Table 2. Characteristics of CVVH

CVVH index	$\bar{x}$ ± SD
Blood (ml/m)	32.5 ± 12.5
Replacement fluid (ml /h)	311 ± 182
Removal (ml/h)	9 ± 16
Heparin (UI/kg/h)	20 ± 11
ACT (seconds)	156 ± 32
Filters	2 ± 1

Comment: The average blood was 32.5 ± 12.5 (ml/ min). Average replacement fluid replacement was 311 ± 182ml/kg/h. Mean heparin concentrations was 20 ± 11UI/kg/h. The mean ACT coagulation time was 156 ± 32s. Each patient used an average of two filters.

Table 3. Changes of pH

Time	pH ($\bar{x}$ ± SD)	Mean	Min	Max	p
T0	7.08 ± 0.2	7.14	6.8	7.35	
T1 = 6 hours	7.17 ± 0.14	7.16	7.01	7.39	T1 & T0>0.05
T2 = 12 hours	7.29 ± 0.12	7.31	7.1	7.44	T2 & T0<0.01
T3 = 24 hours	7.36 ± 0.13	7.42	7.11	7.49	T3 & T0=0.001
T4 = 36 hours	7.41 ± 0.08	7.39	7.28	7.54	T4 & T0=0.001

Comment: Twelve patients with severe acidosis, blood pH was corrected to normal values from decompensated acidosis after 24-hours on CVVH (7.08 ± 0.2 to 7.36 ± 0.13; p<0.01).

Table 4. Changes of NH_3 level

Time	NH_3 (µmol/l) ($\bar{x}$ ± SD)	Mean	Min	Max	p
T0	1052 ± 369	1001	507	1516	
T1 = 6 hours	694.8 ± 268	639	431	1147	T1 & T0>0,05
T2 = 12 hours	429.5 ± 562.4	208.5	50	1347	T2 & T0>0.05

T3 = 24 hours	316 ± 199	361	101	518	T3 & T0<0.01
T4 = 36 hours	198 ± 77	155	109	310	T4 & T0<0.01

Comment: Only 7/19 patients with hyperamonia > 500µmol/l, before CVVH, NH_3 level was 1052 ± 369µmol/L and reduced to the safe level (< 200µmol/L) 198 ± 77µmol/l after 36 hours, statistically significant with p<0.01.

Table 5. Clinical and kidney function changes after CVVH

Index	Before ($\bar{X}$ ± SD)	After ($\bar{X}$ ± SD)	p
GCS (point)	8 ± 1.6	11± 3	0.02
HR (BPM)	149 ± 20	129 ± 22	0.02
Mean ABP	58 ± 16	64 ± 15	0.07
SpO_2 (%)	97 ± 3	96 ± 4	0.38
Urea (mmol/L)	4.7 ± 3.3	1.16 ± 0.89	<0.001
Creatinin (µmol/L)	54.5 ± 19.7	36.7 ± 14.4	0.002

Comment: After CVVH, GCS and HR were decreased with p=0.02, ure and creatinin were decreased with p<0.01.

3.3. Treatment outcome

The average CVVH time was 67.2 ± 44.64 hours, the shortest was 6 hours, the longest was 144 hours.

Complications encountered during continuous CVVH were nosocomial infection 3/19 (15.8%), hypokalaemia 2/19 (10.5%).

The survival rate was 18/19 (94.7%). The mortality rate was 1/19 (5.3%).

4. Discussion

Acute crisis in patients with IEMs occur at any age but the most common in children under 6 months, mean age 10 ± 17 months was smaller than McBryde et al was 56.2 ± 71 months [4]. The smaller the age, the greater the risk of infection, this was one of trigger factor in IEM acute crisis.

Over the world, there were some reseachers reported some papers about the role of CVVH, which treated acute crisis of inborn error of metabolisms. The acute crisis occurs in children with OADs, followed by UCDs, followed by BKD, MSUD (Table 1). In McBryde's study: UCD (14/18), OADs (4/18) [4].

CVVH indication for acute crisis treatment was metabolic acidosis (12/19 patients) and high NH_3 level (> 400µmol/L) (7/19). Arbeiter et al indicated CVVH for acute crisis due to hyperkalemia [5]. McBryde indicated due to organic acids (4/18) [4]. Causes of severe metabolic acidosis were common in patients with organic acidosis, betaketothiolase deficiency, which causes elevated organic acids in the blood, causes decompensation, and destroys brain cells, leading to unstable hemodynamic, persistent metabolic acidosis leading to multiple organ failure resulting in death, MSUD is a chain amino acid IEM, in acute decompensation induced leucine and isoleucine, leading to neurotoxicity, due to the condition of Vietnam is not capable of rapid test of blood amino acids, when the results, patients have severe sequelae, even death. Increased ammonia (NH3) is common in UCDs and OADs, as an emergency in IEMs, elevated NH_3 levels and prolonged cerebral edema, damage to irreversible neurological nerves leading to coma and death. Ammonia should be rapidly reduced as soon as possible to avoid toxicity to brain cells, so CVVH is indicated when blood NH_3 is > 400µmol/l [3].

Our average blood was 5ml/kg/h, which was 9.8 ± 3.4ml/kg/min lower than the Arbeiter's study. The recommended blood rate is 3 - 7ml/kg/min.

The replacement rate of 60ml/kg/h of blood, compared to the recommended rate over 35ml/kg/h, the average burst rate of 9 ± 16ml/h, the patient was able to urinate, the average concentration of heparin was 20 ± 11UI/kg/hour. We relied on ACT (actived cloting time) and kept the ACT for 140 - 160 seconds, ACT at 156 ± 32s, ACT with 230s, so no regular heparin was required after 2 hours ACT, if the trend is still > 160s, continue to stop heparin and check again after 1 hour, generally no bleeding when dialysis. The average filter used was 2, the highest was 5 filters.

CVVH rapidly decreased blood ammonia by convective and diffusional mechanisms, especially in hemodynamically unstable patients. 7/19 patients with hyperamonia before CVVH (1052 ± 369µmol/l), and after 24 hours CVVH the mean blood NH_3 concentration decreased to 316 ± 199µmol/l, statistically significant with $p<0.01$. The pre-CVVH, NH_3 concentration was 1717 ± 1643µmol/l, our patients were mainly OADs, only 4 patients were UCDs, the patients in the Arbeiter study were mainly UCDs, only 2 patients with OADs [5].

The clinical and kidney function tests were changed after CVVH, GCS and HR were decreased with $p=0.02$, ure and creatinin were decreased with $p<0.01$. So CVVH can removed the wastes of the body and corrected mental status. It removed ammonia and creatinin, urea.

18/19 patients survived, accounting for 94.8%, higher than the study by McBryde (42.8%) [4] and Arbeiter (82%) [5]. Our patients were detected and indicated CVVH earlier. After CVVH, the patients improved significantly in mental status, 18/19 patients survived. Mortality from IEMs was 27 - 38%. In our study, only one patient (5.3%) died of sepsis with multiple organ failure. This patient had severe conditions, supported with mechanical ventilation and CVVH, but had bacterial resistance to many antibiotics, despite reduced ammonia levels and improved pH, and had antibacterial therapy with colistine and meronem but did not improve. Nosocomial infection prevention always was the top priority in the intensive care unit, especially in patients with CVVH [6].

The duration of CVVH was 67.2 ± 44.64 hours (6 - 144 hours), longer than McBryde's 39.6 ± 58 hours (2 - 240 days) [4] and Arbeiter et al's 42 ± 30 hours [5], Our patients hospitalized in severe condition, with septic shock and longer CVVH time [6].

The most common complications was nosocomial infection of 3/19 (15.8%), of which one patient died of *Acinetobacter baumannii* resistant to all of the antibiotics. Patients admitted to the hospital in severe condition must have invasive interventions such as mechanical ventilation, intravenous, arterial blood, and urinary catheterizations, so have a higher risk of nosocomial infection. Two patients had hypokalemia in the CVVH process and needed to be corrected.

5. Conclusion

CVVH was effective in the treatment of acute crisis of IEMs, reduced NH_3 to safe levels after 36 hours and corrected pH to normal range after 24 hours with higher survival rate, less complication.

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