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ORIGINAL ARTICLE

Short-term results of continuous venovenous haemodiafiltration versus peritoneal dialysis in 40 neonates with inborn errors of metabolism

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Abstract

Several recent studies have reported that toxic metabolites accumulated in the body as a product of inborn errors of metabolism (IEM) are eliminated more rapidly with continuous venovenous hemodiafiltration (CVVHDF) than with peritoneal dialysis (PD). However, there is still uncertainty about the impacts of dialysis modalities on the short-term outcome. Here, it was aimed to investigate the effects of dialysis modalities on the short-term outcome. This retrospective study included 40 newborn infants who underwent PD (29 patients) or CVVHDF (11 patients) due to inborn errors of metabolism at a tertiary centre, between June 2013 and March 2018. The outcomes and the potential effects of the dialysis modality were evaluated. Of 40 patients, 21 were urea cycle defect, 14 were organic academia, and 5 were maple syrup urine disease. The median 50% reduction time of toxic metabolites were shorter in patients treated with CVVHDF ($p < 0.05$). Catheter blockage was the most common complication observed in PD group (24.1%), whereas in CVVHDF group hypotension and filter blockage were more common. There was no significant difference in mortality between dialysis groups (38% vs. 45.4%, $p > 0.05$). In patients with hyperammonaemia, duration of plasma ammonia > 200 μg/dL was the most important factor influencing mortality (OR 1.05, CI 1.01–1.09, $p = 0.007$).

Conclusion: This study showed that CVVHDF is more efficient than PD to rapidly eliminate toxic metabolites caused by IEM in newborn infants, but not in improving survival.

What is Known:
- *Toxic metabolites are eliminated more rapidly with CVVHDF than with PD.*
- *Higher complication rates were reported with rigid peritoneal catheters in PD and catheter blockage in CVVHDF.*

What is New:
- *Prolonged duration of plasma ammonia levels above a safe limit (200 μg/dL) was associated with increased mortality.*
- *Lower catheter-related complication rates may have been associated with the use of Tenckhoff catheters in PD and the use of right internal jugular vein in CVVHDF.*

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Keywords Continuous venovenous hemodiafiltration · Inborn errors of metabolism · Newborn · Peritoneal dialysis

Abbreviations

aPTT	Active partial thromboplastin time
ASA	Argininosuccinic aciduria
CAVHD	Continuous arteriovenous haemodialysis
CIT	Citrulliaemia
CPS	Carbamoyl phosphate synthetase deficiency
CRRT	Continuous renal replacement therapy
CVVHD	Continuous venovenous haemodialysis
CVVHDF	Continuous venovenous haemodiafiltration
ECD	Extracorporeal dialysis
HD	Haemodialysis
MMA	Methylmalonic acidaemia
MSUD	Maple syrup urine disease
OA	Organic acidaemia
OTC	Ornithine transcarbamylase deficiency
PD	Peritoneal dialysis
PO	Per oral
PPA	Propionic acidaemia
UCD	Urea cycle disorder

Introduction

Neonates with inborn errors of metabolism show non-specific symptoms, such as lethargy, vomiting, hypo/hypertonia, hypoglycaemia, and convulsions, due to the accumulation of toxic metabolites (ammonia and leucine) through nutrition, generally within the first few days after birth [9]. These accumulating toxic metabolites may cause irreversible neurological damage or death [9, 11]. Neurological symptoms, such as urea cycle disorder (UCD) or organic acidaemia (OA), are mainly due to hyperammonaemia [4, 11]. In UCD, partial or complete lack of activity of key enzymes in the urea cycle induces primary accumulation of ammonium and a secondary increase in glutamine production due to the action of intracellular glutamine synthetase in the presence of hyperammonaemia. In OA, intramitochondrial accumulation of acyl-CoA esters induces secondary block of urea cycle enzymes and may result in severe hyperammonaemia [2, 5, 18]. High ammonium levels and excess glutamine accumulation in astrocytes induce cell swelling and brain oedema. The ammonia produced in this way is highly toxic to neural tissue, and delay in removal of ammonia is associated with high rates of morbidity and mortality [11, 22]. In disorders of branched chain amino acid metabolism, such as maple syrup urine disease (MSUD), the accumulation of leucine and its metabolites may cause severe and permanent neurotoxicity. The treatment targets in such diseases are prevention of further toxic metabolite accumulation through nutrition and pharmacological therapy, restoration of metabolic balance, and rapid elimination of accumulated toxic metabolites from the body [3]. In severe cases, or in patients that show an insufficient response to basic treatment, toxic metabolites can be eliminated by peritoneal dialysis (PD) or continuous venovenous haemodiafiltration (CVVHDF) to prevent death or neurological sequelae [6, 12, 19]. Despite it has been reported that toxic metabolites are eliminated more rapidly with CVVHDF than with PD, there is currently no consensus regarding which dialysis method has a more positive effect on prognosis [1, 13, 16].

This retrospective, single-centre, uncontrolled study was performed to analyse the demographic characteristics, including early results and factors that influenced the results, of 40 patients treated with PD or CVVHDF due to inborn errors of metabolism and toxic metabolite kinetics.

Materials and methods

Forty patients monitored in the neonatal intensive care unit between June 2013 and March 2018 who underwent dialysis (PD or CVVHDF) due to inborn errors of metabolism were examined retrospectively. CVVHDF had not been available at the centre during the first 3.5 years of the study period. The following characteristics were recorded: gestational age, birth weight, gender, age, complaints on admission, kinetics of toxic metabolite (ammonia and leucine) levels, dialysis modalities/complications, metabolic defects, and outcome. Blood amino acids, urinary organic acids, and tandem MASS of all cases were examined for diagnosis, and a metabolism expert was consulted. Plasma ammonia level was monitored every 6 h for patients with hyperammonaemia, and plasma leucine level was monitored every 12 h for patients with MSUD.

Two patients who received dialysis due to secondary hyperammonaemia (one case of classic galactosaemia and one case of neonatal haemochromatosis) were excluded from the study.

Supportive treatments

Protein intake was immediately discontinued in all cases. The patients were started on high glucose (10–12 mg/kg/day) and lipid (2 g/kg/day) infusions. Patients with blood glucose levels elevated above 250 mg/dL were started on insulin infusion

(0.05–0.1 units/kg/h), and the infusion was maintained until blood glucose levels decreased below 180 mg/dL. All patients with hyperammonaemia were administered carglumic acid (250 mg/kg loading, 100 mg/kg/day maintenance, per oral [PO]), carnitine (100–200 mg/kg/day, PO), and sodium benzoate (250 mg/kg/day, PO). Protein supply was restarted within 2 days.

Protein limitations were adjusted in UCD patients according to age, clinical status, and laboratory results. Natural protein was added to essential amino acid mixtures (Milupa UCD1; Nutricia, Schiphol, Netherlands), and arginine (250–350 mg/kg/day, PO) was administered. Patients with OA were administered mixtures without precursor amino acids (threonine, methionine, valine, and isoleucine) (Milupa OS1; Nutricia). Patients with propionic acidaemia (PPA) were administered biotin (10 mg/day, PO), whereas methylmalonic acidaemia (MMA) patients received hydroxocobalamin (1 mg/day, intramuscular injection [IM]) [3, 20]. Mixtures without branched chain amino acids (leucine, isoleucine, and valine) (Milupa MSUD1; Nutricia) were used for enteral nutrition in MSUD patients and thiamine (10 mg/day, PO) was administered as an enzyme cofactor [19].

Serum electrolyte disturbance was defined according to the following criteria: hypocalcaemia (calcium < 8.4 mg/dL), hypophosphataemia (phosphorus < 3.8 mg/dL), and hypokalaemia (potassium < 3.5 mmol/L). Calcium gluconate was administered intravenously in cases with hypocalcaemia, and phosphate salt was administered intravenously in cases with hypophosphataemia. In cases with hypokalaemia, potassium chloride was administered with dialysis fluid in patients that received CVVHDF and intravenously in those receiving PD [20].

Patients with convulsions were administered phenobarbital (20 mg/kg loading, 3–5 mg/kg/day maintenance). Mechanical ventilation support was provided for patients with inadequate respiratory ability.

Dialysis

In patients with hyperammonaemia, it was decided to perform dialysis when ammonia level on admission was > 1000 μg/dL, or 500–1000 μg/dL and then kept increasing in the fourth hour of medical treatment. Dialysis was discontinued when the ammonia level dropped below 200 μg/dL. In MSUD patients, dialysis was implemented when two of the following criteria were observed: coma after 3–4 h of medical treatment, gastrointestinal intolerance, and plasma leucine level ≥ 1700 μmol/L. Dialysis was discontinued when the plasma leucine level decreased to < 1000 μmol/L [3, 14].

Peritoneal dialysis

The PD catheter (single-cuff Tenckhoff catheter) was inserted 3–5 cm below the umbilicus by a paediatric surgery specialist under local anaesthesia at the bedside. Peritoneal dialysis was performed with the Baxter dialysis system in cycles of 30–60 min (intermittent). Dialysis was started using fill volumes of 10–20 mL/kg on the first day, increasing to 30 mL/kg on the second day. Standard lactate-buffered solution with glucose concentration of 1.36% was used and switched to 2.27%, in the event of leakage to the extravascular space. The amounts of drained and instilled fluid were recorded in each cycle. Patients were weighed twice a day. All patients were started on intraperitoneal ceftazidime and teicoplanin as antibiotic therapy and were given ampicillin-cefotaxime intravenously. Antibiotic therapy was discontinued depending on culture, clinical, and laboratory results. Peritonitis was defined as the presence of clinical findings and a positive peritoneal fluid bacterial culture.

CVVHDF

A double-lumen 6.5 F catheter was inserted into the right internal jugular vein by a neonatal specialist using the Seldinger technique (in one patient, the catheter was inserted into the left internal jugular vein, as insertion into the right internal jugular vein was unsuccessful). Haemodiafiltration was performed using a Gambro Prismaflex device and HF20 filters (Baxter Healthcare, Deerfield, IL, USA). To prime the extracorporeal blood circuit, erythrocyte suspension (packed red blood cells) was used for patients with pre-dialysis haematocrit < 40%. This was diluted with albumin or 0.9% saline, whereas albumin was used in patients with pre-dialysis haematocrit > 40%. Commercially produced standard solutions were used as dialysate and replacement fluids. Standard solutions included 5000 mL sterile water, 140 mmol/L sodium, 2 mmol/L potassium, 1.75 mmol/L calcium, 111.5 mmol/L chloride, 32 mmol/L bicarbonate, and 6.1 mmol/L dextrose. As an anticoagulant, continuous infusion of unfractionated heparin was begun at a dose of 15 IU/kg/h. The heparin dose was adjusted according to the active partial thromboplastin time (aPTT) and was checked every 6 h. CVVHDF parameters were set as blood flow rate of 10 mL/kg/min, replacement flow rate of 30–50 mL/kg/h, and dialysate flow rate of 2000 mL/1.73 m^2/h. Hypotension was defined as a drop in mean blood pressure > 20 mm/Hg compared to the baseline. The dose was increased in patients who were administered inotrope for hypotension before commencement of CVVHDF. Inotrope was started and the dose was increased when necessary in patients who developed hypotension after commencement of CVVHDF [7, 20].

Statistical analysis

Statistical analyses were performed using the SPSS for Windows (version 15.0) statistical package. The Shapiro-Wilk test was performed to examine the distribution of data. Student's *t* test was used to compare continuous parametric

variables, the Mann-Whitney *U* test was used to compare continuous nonparametric variables, and chi-square test or Fisher's exact tests were used for categorical variables when appropriate. Only variables found to be significantly different between survivors and non-survivors were included in the multivariable logistic regression analysis to identify independent risk factors for mortality. The performance of those factors in predicting NICU mortality was determined by the area under the receiver operating characteristic (ROC) curve and the best cutoff (break-point) values were calculated using *Youden* index. The results of the logistic regression were presented as odds ratios (OD) and their 95% confidence intervals (CIs). A two-tailed p value of < 0.05 was considered to be statistically significant. Parametric continuous variables are expressed as mean ± standard deviation, nonparametric continuous variables are expressed as the median (interquartile range), and categorical variables are expressed as numbers (%).

Results

Of the 40 patients included in the study, 21 had UCD (citrulliaemia [CIT], $n = 10$; ornithine transcarbamylase deficiency [OTC], $n = 5$; argininosuccinic aciduria [ASA], $n = 3$; carbamoyl phosphate synthetase deficiency [CPS], $n = 2$; and no type diagnosis, $n = 1$), 14 had OA (MMA, $n = 7$; PPA, $n = 5$; and no type diagnosis, $n = 2$) and five had MSUD. All patients were full-term newborn infants without any postnatal problems who had been fed with breast milk or formula from the first day. Thirty-four of the patients had been referred to our hospital from other centres, whereas only six had been admitted directly to our clinic. The demographic and clinical characteristics of the groups are shown in Table 1. In the subgroup analyses based on the type of the metabolic diagnosis (Table 2), it was found that the median duration of dialysis, 50% ammonia reduction time, and the median duration of plasma ammonia > 200 μg/dL were shorter in the patients with UCD who treated with CVVHDF than those treated with PD. However, the same variables could not make a statistically difference between dialysis modalities in the patients with OA, as only one of them had treated with CVVHDF. In PD group 7 patients, and in CVVHDF group, two patients died during dialysis. There was no death in patients with MSUD.

Univariate analyses revealed that lower age at admission and having UCD as type of metabolic disorder were associated with higher mortality rate while assessing all patients. In patients with hyperammonaemia, pre-dialysis ammonia levels, time of 50% ammonia reduction, and the duration of plasma ammonia level > 200 μg/dL were higher in non-survivor group (Table 3). In multivariate logistic regression, the duration of plasma ammonia level > 200 μg/dL was the most important factor influencing mortality in patients with hyperammonaemia (OD 1.05, CI 1.01–1.09, $p = 0.007$). Its performance in predicting the NICU mortality using ROC curve yielded an area under ROC curve of 0.78 (95% CI, 0.626 to 0.940), with break-point of 43th hour of dialysis (sensitivity 75%, specificity 73.7%, for mortality). There was not any association between complications and mortality (complication was seen in 33.3% of survivors, and in 43.8% of non-survivors, $p > 0.05$).

Dialysis modalities and complications

In 7 of the 29 patients who received PD, the PD catheter was obstructed and needed to replace. One patient developed peritonitis and recovered fully with antibiotic therapy. Bleeding from where the catheter placed was detected in one patient with haemorrhagic diathesis, but the bleeding was stopped by supportive treatments. Severe hypotension or serum electrolytes abnormality was not observed in any patients.

Five patients in the CVVHDF group developed hypotension requiring inotrope and volume support. The aPTT values were elevated in five patients. Two of those patients received fresh frozen plasma, because of the target values could not be reached by lowering the heparin infusion dose. Dialysis filters were changed due to blockage within the first 12 h of dialysis in all three patients in whom erythrocyte suspension was used to prime the extracorporeal blood circuit. Three patients developed hypocalcaemia and hypophosphataemia, whereas two patients developed hypokalaemia. Vitamin D deficiency was detected in one patient whose hypocalcaemia persisted despite supportive treatment. Hypocalcaemia was completely corrected with high doses of vitamin D and calcium gluconate supplementation. In the both dialysis groups, there was no an association between complications and mortality.

Discussion

This study compared the short-term results in patients treated with PD or CVVHDF due to IEM in the neonatal period. The results indicated that toxic metabolites were eliminated more rapidly by CVVHDF than PD, and that dialysis modality had no effect on mortality. The duration of plasma ammonia level > 200 μg/dL seemed the most important factor influencing mortality in patients with hyperammonaemia. Limited studies comparing CVVHDF and PD in neonatal patients [1, 16, 23] make this study one of the largest single-centre ones using a single protocol to compare patients undergoing PD or CVVHDF due to intoxication-type IEM in the neonatal period.

There is no doubt that early diagnosis and emergency treatment have considerable effects on the prognosis of metabolic diseases, including toxic metabolite accumulation. Urgent PD or extracorporeal dialysis (ECD) should be initiated in patients with poor responding to nutrition and pharmacological

Table 1 The demographic and clinical characteristics of the patients

Feature	PD ($n = 29$)	CVVHDF ($n = 11$)	p
Baseline characteristics			
Male gender	14 (40.8)	5 (45.5)	0.873
Birth weight, g	3000 (2830–3050)	3050 (2900–3200)	0.266
Age at admission, days	4 (3–8)	3 (2–6)	0.239
Symptoms on admission			
Poor feeding	18 (62.1)	6 (54.5)	0.665
Vomiting	4 (13.8)	1 (9.1)	0.688
Seizure	10 (34.5)	4 (36.4)	0.911
Apnoea	8 (27.6)	2 (18.2)	0.540
Respiratory	17 (58.6)	7 (63.6)	0.772
Arterial blood gases			
pH	7.17 ± 0.23	7.3 ± 0.2	0.336
HCO_3^-, mmol/L	16.6 ± 7.8	21.5 ± 5.9	0.074
Base excess, mEq/L	−10.4 ± 10.1.	−6.3 ± 6.9	0.224
The need for mechanical ventilation	12 (41.3)	10 (90.9)	0.211
Duration of mechanical ventilation, days	2.5 (2–6)	3.5 (2.75–5.25)	0.407
Clinical characteristics			
The type of metabolic defect			
MSUD, *n* (%)	3 (10.3)	2 (18.2)	0.603
OA, *n* (%)	13 (44.8)	1 (9.1)	0.061
UCD, *n* (%)	13 (44.8)	8 (72.7)	0.162
Time to start dialysis after admission, h	7 (5–8.5)	6 (4–11)	0.807
Duration of dialysis, h	60 (24–120)	48 (24–72)	0.144
Pre-dialysis ammonia levels, μg/dL	1652 (1082–2744.5)	3200 (1761–4472)	0.083
Time of 50% ammonia reduction, h	14 (6–30)	6 (6–9.5)	*0.01*
Duration of plasma ammonia > 200 μg/dL, h	33 (21–84)	44 (27–52)	0.895
Pre-dialysis leucine levels of all patients, μmol/L	2440, 3600, 4667	2430, 2600	-[†]
Leucine levels at the 12th of dialysis, μmol/L	1700, 3000, 2347	825, 900	-[†]
Short-term outcome			
Complication	8 (27.5)	6 (54.5)	0.65
Death	11 (38)	5 (45.4)	0.665

Statistically significant values are shown in italics. Data are expressed as mean ± SD, median (interquartile range), or number (%)

[†] Because of small number of patients, statistical analysis was not performed

treatment [3]. Thorough technological progress, ECD is increasingly used in neonates and is currently recommended as the first choice, especially at centres manage widely metabolic diseases [1, 15, 16, 19]. Recent studies have indicated that ECD reduces the duration of dialysis, eliminates toxic metabolites more rapidly, and so, it has been expected to have a more favourable impact on prognosis than PD [1, 19]. Moreover, even among ECD modalities, different results have been reported. A number of studies have suggested that intermittent haemodialysis (HD) is more effective than other dialysis modalities [21]. In another study [16], it was found there was no difference among various ECD modes, i.e. continuous venovenous haemodialysis (CVVHD), continuous arteriovenous haemodialysis (CAVHD), or HD.

In a large series included newborn infants, Picca et al. reported that plasma ammonia levels were eliminated more rapidly from the body by ECD, and that the highest mortality rate was seen in patients with UCD, having no effect of dialysis modality (ECD vs. PD) on short-term prognosis [16]. The similar finding has also been reported by Arbeiter et al. [1], which the half-life time of ammonia was significantly shorter in infants treated with CVVHD than those treated with PD. Additionally, they noted that there was no difference between two dialysis modalities in the time of lowering plasma ammonia to a safe level (< 200 μg/dL). In the study presented here, it was found that CVVHDF eliminated toxic metabolites from the body more rapidly, with shorter duration of dialysis. Despite it was not statistically significant, it seemed that

Table 2 Comparison of dialysis modalities based on subgroup analyses

Variable	Urea cycle disorder			Organic acidaemia*		$p^{\dagger}$
	PD[†] ($n = 13$)	CVVHDF ($n = 8$)	p	PD [†] ($n = 13$)	CVVDHF ($n = 1$)	
Pre-dialysis ammonia levels, μg/dL	1813 (1058–2604)	3665 (2110–4608)	0.051	1641 (1169–3820)	2097	0.858
Time of 50% ammonia reduction, h	30 (11–67)	6 (6–12.5)	*0.007*	7 (6–13.5)	6	*0.007*
Duration of plasma ammonia > 200 μg/dL, h	72 (45–104)	46 (33–53)	0.053	24 (15–30)	15	*0.005*
Duration of dialysis, h	96 (48–132)	48 (30–66)	*0.033*	48 (24–54)	48	*0.024*
Death	7 (53.8)	5 (62.5)	1	4 (30.7)	0	0.428

[†] Among patients underwent peritoneal dialysis, those with urea cycle disorder and those with organic acidaemia were compared

*Because of only one patients with organic acidaemia had been treated with CVVHDF, the analysis was not made between the groups

Statistically significant values are shown in italics. Data are expressed as median (interquartile range), or number (%). *PD*, peritoneal dialysis; *CVVHDF*, continuous venovenous hemodiafiltration; *g*, gram; *h*, hour

duration of plasma ammonia > 200 μg/dL in patients with UCD was slightly longer in the PD group than in the CVVHDF group. On the other hand, PD was likely to more rapidly eliminate ammonia with shorter duration of dialysis in patients with OA when compared to those with UCD. That might be explained by extremely high ammonia production in UCD, requiring more effective modality to reduce plasma ammonia levels (e.g. CVVHDF).

In this study, it was found that there was no statistically difference in mortality between the groups. In total, the higher rate of mortality in this study, when compared to previous studies [16, 19, 21], might be the result of the fact that most patients in this study were referred from other centres, and therefore, it was likely to lead to a delay in diagnosis and prompt treatment. We thought that the limited facilities for diagnosis of IEM and unavailability of PD in the many centres dealing with caring newborn infant in the region led to a prolonged the time to initiate medical and dialysis treatment, which probably indicates the major determinant of outcome [16]. Similar to previous studies [3, 8, 13, 14], in the present study, the mortality rate was higher in patients with UCD than in patients with OA or MSUD. That is probably due to higher ammonia generation in this type of metabolic disorder, which leads to longer hyperammonaemic state. In a large series including 45 hyperammonaemic neonates treated with different dialysis modalities [16], mortality rates were reported as 17.4% in the PD group and 40.9% in the ECD (CAVHD, CVVHD, or HD) group, without showing statistically significance. They concluded that the late referral of patients reduced the superiority of ECD to PD in improving the short-term outcome of hyperammonaemic newborn infants. Short-term outcome of patients with MSUD, in our study, was favourable in both dialysis modalities; however, longer duration of leucine removal in the PD group may increase the risk of irreversible damage to the brain.

It has been reported that the clinical outcome of patients with hyperammonaemia due to IEM might be affected by pre-dialysis plasma ammonia levels, duration of coma, the type of metabolic disorder causing hyperammonaemia, and prompt diagnosis and treatment [13, 15, 16, 19]. In recent studies, however, the associations of pre-dialysis plasma ammonia levels and the rate of ammonia removal with patient outcome

Table 3 The factors affecting mortality

Variables	Survivors ($n = 24$)	Non-survivors ($n = 16$)	p
Age at admission, days	5.5 (3–9)	3(3–7.5)	0.010
The type of metabolic disorder (UCD)	9 (37.5)	12 (75)	0.027
Patients with hyperammonaemia	$n = 19$	n = 16	
Pre-dialysis ammonia levels, μg/dL	1425 (1033–2097)	2760 (1499–4630)	0.012
Time of 50% ammonia reduction, h	6 (6–12)	14 (11–57)[†]	0.003
Duration of plasma ammonia > 200 μg/dL, h	30 (18–48)	55 (38–107)	0.004*
Plasma ammonia > 200 μg/dL after the 43th hour of dialysis, *n*	5 (26.3)	12 (75.0)	0.007

UCD urea cycle disorder

[†] Two patients died at 36 and 48 h of dialysis, before ammonia dropped to a half of pre-dialysis level

*In the model using logistic regression analyses it was revealed that plasma ammonia > 200 μg/dL after the 43th hour of dialysis was associated with mortality in patients with hyperammonaemia (odds ratio 8.4, 95% confidence interval 1.83–38.6, $p = 0.006$)

have not been established [16, 22]. In a study conducted by Enns et al. [8], it was reported that mortality rate in patients with UCD raised from 20 to 35% in the presence of coma. Pela et al. reported that the durations of coma and the type of metabolic disease were the most important factors affecting prognosis, and suggested that PD still remains a useful treatment option, particularly in patients with OA [13]. Given the retrospective nature of the study presented here, unfortunately, duration of pre-dialysis coma was not able to be calculated due to the absence of reliable data. So, it was not possible to assess any relationship between coma and outcome. We found that younger age at admission, which means that the clinical manifestation presents in the early days of life, and the type of metabolic disorder, particularly UCD, were associated with mortality in patients undergoing dialysis. Additionally, in patients with hyperammonaemia, pre-dialysis ammonia levels, time of 50% ammonia reduction, and the duration of plasma ammonia level > 200 μg/dL seemed to have an effect on mortality. Of them, the last one was the most influencing factor, especially when this time exceeds 43 h the risk of mortality was folded eight times. Considering that findings, lowering plasma ammonia levels to a safe limit by an efficacious dialysis modality seems to be crucial. However, the effect of the rapidity of plasma ammonia removal by dialysis modalities on mortality has not been clarified yet [18, 21, 22]. It has been suggested that when PD was initiated rapidly following the first symptoms of hyperammonaemic coma in where other modalities are not available, patient outcome is likely to be favourable [13]. On the other hand, efficacy of dialysis with other modalities can be reduced by late referral, longer time to initiate dialysis, and pre-dialysis poor clinical status [18, 21, 22]. Because of the duration of neonatal hyperammonaemic state, which means the exposure of developing brain to toxins, is crucial for long-term outcome [19], the main objective should focus on approaches that will shorten this period. Therefore, in addition to medical treatment, PD can be initiated as a temporising measure till accessing to a centre where ECD (e.g. CVVHD) is available. It should be kept in mind that there are certainly some other factors such as catabolic state of the patient, the level of residual enzyme activity, the presence of co-existing factors (e.g. hypoglycaemia, acidosis, renal impairment, hemodynamic instability) may influence either the efficacy of therapeutic interventions or outcome.

Complications including serum electrolyte abnormality, haemodynamic instability, haemorrhage, and catheter blockage have been commonly reported in patients treated with CVVHDF, particularly in neonates [1, 15, 19, 20]. In our study, hypotension, filter blockage, and some serum electrolyte abnormalities were the most common complications in the CVVHDF group. During CVVHDF, the loss of time due to filter blockage has a negative impact on the efficient and rapid elimination of toxic metabolites [13, 17]. In this study, filter blockage was observed in three patients in whom erythrocyte suspension had been used to prime the extracorporeal blood circuit, suggesting a possible association between both. In contrast to previous reports [1, 20], catheter blockage did not develop in our cases treated with CVVHDF. In those studies, catheter insertion into certain anatomical sites was associated with higher frequency of blockage. However, in our study, in addition to using relatively large catheter, the use of right internal jugular vein as the site of catheter insertion in all patients, except one, seemed to provide a longer time for patency of catheter. Depending on its anatomical localisation, the right internal jugular vein enables a shorter intravenous catheter length and a straighter anatomical line, which may prevent catheter blockage. In the PD group, the rate of catheter blockage was 24.1%, which seemed to comparable to those reported in the literature [3, 10]. That rate was likely achieved by thank to the use of the Tenckhoff catheter which associated with less catheter-related complications [10, 19]. Because of such problems may result in prolonged time of toxin removal, in case of severe hyperammonaemia PD should only be considered as a temporary measure to avoid a delayed ECD until the transfer of the patient to referral centre is completed. On the other hand, PD seems to improve outcome of patients with less severe hyperammonaemia deriving from IEM rather than UCD, and with MSUD.

There were several limitation in the study presented here. First, despite the number of patients in this study was relatively high, it was not enough homogenous to enhance the power of statistical analyses. We think that some marginal associations would have been significant if the numbers were a bit more. Second, given the retrospective nature of this study, the accessibility of some needed variables may have been problematic during data collection, and consequently, this might led to the difficulty in the evaluation of temporal relationships between events. Third, the character of data from single centre may limit the representative of other geographical areas or institutions. Finally, long-term outcome could not be evaluated due to inability to reach a significant number of patients who survived. Despite these limitations, we suggest that this study has contributed to our knowledge about dialysis treatment of newborn infants with intoxication-type IEM.

In conclusion, this study showed that toxic metabolites deriving from IEM during metabolic crisis in the neonatal period can be eliminated more rapidly with CVVHDF than with PD, without making a significant difference on mortality. Prolonged duration of plasma ammonia > 200 μg/dL in newborn infants with hyperammonaemia seemed to increase the risk of death, and probably risk of neurological damage in survivors. Despite medical treatment once dialysis is indicated, even if ECD is not available or while being waited for transferring, PD should be initiated to shorten the time exposure of the brain to toxic metabolites.

Authors' contributions M.C.: conception, analysis of data, write the first draft of the manuscript, the literature search and full text acquisition; O.A. and N.O.: analysis of data, literature search, and revise the manuscript; M.S.I and M.N.O.: cross-check the data, appraise the quality of the studies; all authors contributed important intellectual content in drafting and revising the manuscript and approved the final version for submission.

Compliance with ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by Clinical Research Ethics Board (Registration Number: 29/12/2017-108).

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Written informed consent was obtained from all parents' individual participants included in the study.

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