Comparison of The Peritoneal Dialysis and Continuous Veno-Venous Hemodiafiltration in 16 Neonates With Maple Syrup Urine Disease

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Diyarbakır children hospital

Research Article

Keywords: CVVHDF, MSUD, Newborn, Peritoneal dialysis.

Posted Date: August 30th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-780920/v1>

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Abstract

Introduction: Continuous Renal Replacement Therapy (CRRT) is a well-known treatment modality for patients with acute renal failure and has been increasingly used for the treatment of metabolic disorders such as Maple Syrup Urine Disease (MSUD) in recent years. Herein, we aimed to discuss our experience in 16 newborn patients with MSUD who were treated with urgent renal replacement therapy (RRT).

Materials and Method: The data of patients who presented with an acute metabolic crisis due to Maple syrup urine disease and who were treated with RRT at Neonatal intensive care unit(NICU) between November 2016 and March 2020 were retrospectively evaluated. The patients underwent continuous veno-venous hemodiafiltration (CVVHDF) or peritoneal dialysis (PD) as renal replacement therapy.

Results: The study enrolled a total of 16 patients, of which 8 were male and 8 were female. Eleven (68.75%) patients underwent CVVHDF and five (31.25%) underwent peritoneal dialysis. The median post-treatment leucine level was 198(20-721) $\mu\text{mol/L}$ in the CVVHDF group and 1050(303-1653) $\mu\text{mol/L}$ in the PD group; the median leucine reduction rate per hour was 2.56% (1.75-7.6) in the CVVHDF group and 0.78% (0.54-1.83) in the PD group. There was a significant difference between both groups regarding both parameters ($p=0.08$, $p=0.001$, respectively). Complications such as hypotension, electrolyte imbalance, and filter obstruction occurred in the CVVHDF group while catheter revision was needed due to catheter obstruction in one patient in the PD group.

Conclusion: This study showed that CVVHDF is more effective than PD for rapidly eliminating elevated Leucine levels caused by MSUD in the newborn and it is not associated with increased complication rates.

What Is Known

Maple Syrup Urine Disease is one of the serious health problems in newborn babies. Peritoneal dialysis is frequently used. However, the use of Continuous veno-venous hemodiafiltration therapy is increasing steadily.

What is New: Leucine levels were more rapidly eliminated by the CVVHDF than PD and that CVVHDF did not increase mortality.

Introduction

Maple syrup urine disease (MSUD) is a congenital metabolic disease that results from the disordered metabolism of branched-chain amino acids(BCAA) valine, isoleucine, and leucine[1]. It is an autosomal recessive disorder that occurs due to the reduced activity of the branched-chain alpha-ketoacid dehydrogenase complex found in mitochondria[1]. Elevated serum levels of leucine and its metabolites impair brain development and growth, leading to neurological symptoms[2]. Leucine metabolites cause apoptosis in both glial and neuronal cells[2]. When the disease is suspected, plasma amino acids should be investigated to detect increased serum levels of branched-chain amino acids and isoleucine (a leucine metabolite) [3]. In children who have suspected disease due to family history or who undergo neonatal screening, appropriate nutritional management beginning in the first hours of life can prevent the development of neurological injury[3]. Early treatment is essential for preventing neurotoxicity and death[3]. The golden period for initiating therapy before irreversible neurological injury occurs is the first 7–10 days[3]. Renal replacement therapy (RRT) methods have been increasingly used for congenital metabolic disorders. The ultimate goal is to effectively remove toxic metabolites and to minimize the duration of exposure to those metabolites while the diagnostic studies are performed. Renal replacement therapy modalities include peritoneal dialysis (PD), intermittent hemodialysis (IHD) and continuous veno-venous hemi filtration (CVVH), continuous veno-venous hemodialysis (CVVHD), and continuous veno-venous hemodiafiltration (CVVHDF) [4]. Among these, CVVHDF and PD are the most commonly used methods. Hemodiafiltration is the best method for removing toxic metabolites; however, peritoneal dialysis can also be utilized as an alternative in centers where hemodiafiltration cannot be performed[5].

The aim of the present study was to compare the effectiveness of CVVHDF and PD for acute detoxification in the newborn with MSUD.

Materials And Method

This study retrospectively evaluated the medical records of patients who were diagnosed with MSUD and treated with RRT at Diyarbakır Pediatric Hospital Neonatal Intensive Care Unit between 01 March 2016 and 20 March 2020.

Study Inclusion Criteria:

Patients admitted to and treated at the neonatal intensive care unit, who were:

Diagnosed with MSUD

Treated with RRT

Born at a gestational age of 37 to 42 weeks

Born with a birth weight of ≥ 2000 g

Study Exclusion Criteria:

Infants with:

Multiple congenital anomalies

Chromosomal disorders

Cyanotic congenital heart disease

Neural tube defects

Birthweight < 2000 g

The medical records of infants with MSUD who had been admitted to the Neonatal Intensive Care Unit and treated with RRT during the specified time window were obtained. The medical data of the study patients were obtained from their medical records kept in the hospital's archive unit. A form was prepared for each case, which included the infants' demographic characteristics, birth weight, birth week, gender, length of hospital stay, RRT outcomes, as well as leucine, isoleucine, and valine levels and the other biochemical, hemogram, and coagulation parameters in the first 24 hours and during RRT.

Catheterization

Internal jugular or femoral veins were used for central venous catheterization (SVC). A 6.5-7 Fr (Arrow; Arrow International, Reading, Pennsylvania, USA) double-lumen hemodialysis catheter was used. During catheterization, asepsis criteria were complied with and sedoanalgesia was induced. Ultrasonography was used whenever necessary. The catheters were placed using the Seldinger Technique and fixed to the skin. Gambro Prismaflex device and HF20 filters (Baxter Healthcare, Deerfield, IL, USA) were used for hemodiafiltration in 11 patients. Five patients underwent peritoneal dialysis. Commercially produced standard solutions, dialysates, and replacement fluids were used. Standard solutions contained 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.

Continuous Veno-Venous Hemodiafiltration

The following CVVHDF settings were used: blood flow rate 10–20 mL/kg/min, replacement flow rate 30–50 mL/kg/hour, and dialysate flow rate 2000 mL/1.73 m²/hour. Anticoagulation was achieved by unfractionated heparin which was initially administered as a continuous infusion at a rate of 10 IU/kg/hour and then adjusted to an aPTT (activated partial thromboplastin time) of 60–80 seconds during follow-up. The goal was to keep aPTT 1.5 times normal. When aPTT was 2 times normal, heparin dosage was reduced. Blood samples were collected from all patients every 4 hours to check blood gases, electrolytes, PT, and aPTT. Blood amino acid levels were checked every 12 hours. Serum phosphorus level of less than 4 mg/dL was considered hypophosphatemia. Serum corrected calcium level of less than 8 mg/dL was considered hypocalcemia. Patients who developed hypophosphatemia and hypocalcemia were administered intravenous phosphorus and calcium supplementation. It was attempted to keep serum calcium level at 8–11 mg/dL and serum phosphorus level at 4–8 mg/dL. Patients who developed hypotension after the initiation of CVVHDF were begun on inotropes and their dosage was increased as needed.

Peritoneal Dialysis

Peritoneal dialysis catheter (single cuff Tenckhoff catheter) was placed by a pediatric urologist 3–5 cm below the umbilicus under local anesthesia at the bedside. Peritoneal dialysis was performed in 30–60-minute (intermittent) cycles using the Baxter dialysis system. Dialysis was carried out using filling volumes of 10–20 mL/kg on the first day, which were increased to 30 mL/kg on the second day. The fluid amounts that were introduced and removed were recorded for each cycle. The patients were provided with hypercaloric parenteral nutrition (110–130 kcal/kg/day) and oral thiamin supplementation (10 mg/kg/day) via an orogastric catheter. Intravenous fluids containing a high amount of dextrose (rate 10–12 mg/kg/min) and intravenous lipid emulsions (rate 1–2 g/kg/day) were commenced to reach an anabolic state. In MSUD, renal replacement therapy was started when the patients developed coma, gastrointestinal intolerance, worsening clinical condition, inability to feed, and a plasma leucine level of ≥ 1700 μ mol/L after a 4-hour medical treatment. When plasma leucine level dropped below 1000 μ mol/L, renal replacement therapy was stopped.

Calculations

At the end of the renal replacement therapy, the Leucine reduction rate percentage achieved was calculated according to the formula: (pre-treatment leucine – post-treatment leucine/pre-treatment leucine) $\times$ 100[6].

Leucine reduction rate percentage per hour was calculated according to the formula: leucine reduction rate percentage achieved/treatment hours[7].

The study was approved by Dicle University Ethics Committee (03.06.2021/314).

Statistical Analyses

Study data were analyzed using SPSS statistical software package. Quantitative variables were presented as median (minimum-maximum) and categorical variables as number (n) and percentage (%). Since the parametric test assumptions were not met, the Mann-Whitney U test was used to compare the means of two independent groups. A p-value of less than 0.05 was considered statistically significant.

Results

Eight (50%) patients were female and 8 (50%) were male. Eleven (68.75%) patients underwent CVVHDF and 5 (31.25%) underwent peritoneal dialysis. The median age was 13 (7–28) days in the CVVHDF group and 9 (7–28) days in the PD group. The median weight on admission was 3370 g (2750–3930) g in the CVVHDF group and 3000 (2150–3780) g in the PD group. The median gestational week was 39 (37–42) weeks in the CVVHDF group and 40 (39–41) weeks in the PD group. The demographic characteristics and treatment options were shown in Table 1; the comparison of the means of continuous variables by treatment modality was shown in Table 2 and Figs. 1, 2, and 3. According to the comparison of the means of continuous variables by treatment modality,

there was a significant difference between the CVVHDF and PD groups with respect to mean dialysis duration, post-treatment leucine level, and leucine reduction rate per hour ($p < 0.05$) whereas no significant difference was found regarding the pre-treatment leucine level and leucine reduction rate ($p > 0.05$). Among 10 (90%) patients who underwent CVVHDF, the right internal jugular vein was used as the catheter entry site in seven patients, the left internal jugular vein in 3 patients, and the right femoral vein in 1 (10%) patient. Hypotension was defined as a drop of > 20 mmHg in mean arterial pressure compared to baseline or a mean arterial pressure below 3 percentiles by gestational week. Six (54.5%) patients received inotropic support prior to CVVHDF due to hypotension. Filter replacement was performed in 2 (18%) patients due to filter obstruction. Hypothermia was defined as a body temperature of less than 36.50 °C; one patient who underwent CVVHDF developed hypothermia, whose incubator temperature was increased and normothermia was achieved.

Discussion

This study enrolled patients who underwent peritoneal dialysis or CVVHDF as a CRRT method. As far as we know, our study is the largest newborn study to date that compared the PD and CVVHDF methods in MSUD. Our results indicated that leucine levels were more rapidly eliminated by the CVVHDF than PD and that CVVHDF did not increase mortality.

Maple syrup urine disease presents with coma in the newborn period; accumulation of toxic metabolites, especially leucine and its metabolites, causes acute metabolic crisis, severe neurological and developmental injury, or even death[1, 8]. It has been shown that cerebral leucine accumulation causes neurotransmitter consumption and replaces other essential amino acids, leading to impaired normal brain growth and development; thus, its levels should be effectively lowered as quickly as possible[9]. Patients may present with inability to suck, poor feeding, intolerance to feeding, vomiting, hypotonia, apnea, respiratory failure, and convulsions[4, 5]. Infants with MSUD are at risk of metabolic decompensation and should be treated with an emergency protocol[9]. The goal of acute therapy is to reduce catabolism and to increase protein anabolism[9]. Severe cases should be aggressively treated (e.g. dialysis, hemofiltration, parenteral feeding, and/or orogastric feeding) [9]. The acute dietary therapy should be aggressive and contain adequate energy (up to 150% of normal energy expenditure) provided by a formula, which is free of BCAA, and fluids[9]. The most common cause of admission among our patients was feeding problems and respiratory failure. In these patients, as the leucine reduction rate per hour increases, the time to starting complete enteral feeding decreases.

Lowering the concentrations of BCAA and their metabolites can prevent neurological injury and save lives[5]. Patients need a rapid diagnosis and urgent elimination of toxins with specific therapy[1]. In recent years, recommendations about the use of CVVHDF have been increasing thanks to technological advances and to an increasing, albeit still limited, number of case reports discussing the CRRT methods[5, 7, 10]. Renal replacement therapies have been successfully used to lower the plasma levels of low molecular weight substances[7]. While peritoneal dialysis has been frequently used in the newborn, the rate of using intermittent hemodialysis (IHD) and continuous hemofiltration methods has been constantly rising[7, 10]. In newborn babies, it may be difficult to perform CRRT due to difficulties related to catheter placement and hemodynamic instability[10]. In our unit, five patients with a failed catheter placement attempt had to undergo PD. Peritoneal dialysis has a limited capacity to increase renal clearance and to remove the solute burden and fluid overload, which makes CRRT a more favorable method[7]. Phan et al[7]. showed the efficacy of IHD in acute MSUD crisis in children. However, IHD may lead to a greater rate of hemodynamic instability[7, 8, 10]. Arterial blood pressure and cerebral blood flow disorders may increase the extent of neurological injury[7, 8, 10]. Newborn infants are more susceptible to this side effect[10]. In MSUD, leucine levels may increase if the catabolic process persists or when they show a rebound increase after IHD[5, 7, 10]. It is believed that thanks to allowing a safer electrolyte replacement and a lower risk of rebound leucine increase, CVVD, CVVHD, and CVVHDF, among other continuous modalities, may offer an advantage over IHD[7, 10, 12, 13]. There has been a recent increase in the number of studies that dealt with the technique and frequency of RRT[5, 10–12]. Studies on patients with congenital metabolic disorders have shown that CVVHDF was effective and provided a rapid reduction in toxic metabolites[1, 14]. Jouvett et al[15]. compared the three methods (CVVHDF, CVVH, and CVVHD) in three infants with MSUD and demonstrated that CVVHDF was more effective in eliminating leucine. Kornecki et al[16]. showed that leucine levels more rapidly fell with CVVHDF compared with CVVH. Çelik et al[5]. reported that the short-term outcomes of patients with MSUD were favorable with both dialysis methods, although longer leucine exposure with PD may increase the risk of irreversible brain injury. There are a limited number of studies, mostly in the form of case reports, examining acute detoxification therapy in newborn infants with MSUD[5, 10, 15].

Since leucine is not an osmotic molecule, its rapid removal does not cause any problem; furthermore, since brain blood flow is constant, there is no risk of brain edema[10]. However, CRRTs are associated with several complications. Previous studies have widely reported a number of complications in patients treated with CVVHDF, particularly in the newborn, such as serum electrolyte abnormalities, hemodynamic instability, hemorrhage, and catheter obstruction[17, 18]. In our study, 11 (68.75%) patients received mechanical ventilation support. Hypotension, filter obstruction, and some serum electrolyte abnormalities were the most common complications in our study. Six of 11 patients who underwent CVVHDF developed hypotension, three patients hypokalemia, one patient hypothermia, and two patients filter obstruction in dialysis set, while one patient underwent SVC replacement due to catheter obstruction. A patient in the PD group underwent catheter revision due to obstruction. Eight (72.7%) patients in the CVVHDF group and 3 (60%) in the PD group received mechanical ventilation support. Our study did not find any significant difference between the CVVHDF and PD groups with regard to the leucine reduction rate. However, the leucine reduction rate per hour was significantly higher in the CVVHDF group than in the PD group ($p < 0.05$). These results indicate that CVVHDF is much more effective than PD in newborn MSUD patients. However, one must exercise caution about hypotension and electrolyte imbalance; additionally, when a patient develops hypothermia, body temperature should be carefully observed. One of our patients died in the second week after RRT.

Limitations

Our study had some limitations. Firstly, it was a single-center study with a limited number of patients. Secondly, patients treated with HDF were treated only with the CVVHDF method. We could not compare the effectiveness of different treatment methods. Thirdly, there may have been some errors related to data accessibility and collection owing to the retrospective nature of the study. As a final limitation, long-term outcomes could not be assessed due to the inability

to reach the surviving patients. Despite these limitations, we believe that this study contributed to the literature about the treatment of newborn infants with MSUD.

Conclusion

In conclusion, we believe that CVVHDF is the most effective treatment method for the treatment of acute metabolic crisis of MSUD in the newborn period when used in conjunction with nutritional support and general medical therapies. Continuous veno-venous hemodiafiltration rapidly and safely eliminates leucine levels. Still, caution should be exercised about several complications of the method during its use, such as hemodynamic instability, electrolyte imbalance, hypothermia and filter obstruction. There is a need for comprehensive studies involving larger patient populations in order to implement this method as a standard protocol.

List Of Abbreviations

CRRT

Continuous Renal Replacement Therapy, MSUD; Maple Syrup Urine Disease, RRT; Renal replacement therapy, NICU; Neonatal intensive care unit, CVVHDF; Continuous veno-venous hemodiafiltration, PD; Peritoneal dialysis.

Declarations

Compliance with Ethical Standards

Funding: N/A

Conflict of interests/Competing interests: N/A

Ethical approval and consent to participate: Our study received ethics approval from the Dicle University Medical Faculty non-interventional clinical studies ethics committee, Diyarbakır, Turkey (03 June 2021/314).

Consent for publication: N/A

Availability of data and material: N/A

Code availability: N/A

Disclaimer: N/A

Authors' contributions: All authors fulfil the criteria for authorship; I.D, M.Ç and I.T. initiated the study; I.D, M.Ç and I.T. Collected the data; I.D, M.Ç and S.S. analysed the data; I.D and M.Ç. Interpreted the data; I.D, M.Ç, S.S and I.T.drafted the report. All authors commented on the drafts and have seen and approved the final version.

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Tables

Table 1
The demographic and clinical characteristics of the patients

Patient	Sex	Weight at admission (gram)	Age at admission (days)	RRT modality	Dialysis time (hour)	Initial plasma leucine (μmol/L)	Final plasma leucine (μmol/L)	Complication	Intubation	Leucine reduction rate % achieved	Leucine reduction rate % per hour	Symptoms at admission
1	Female	3600	10	CVVHDF	24	5796	482	No	Yes	91.6	3.8	Po-fee vor res fai
2	Male	3380	20	CVVHDF	12	2300	190	No	Yes	91.7	7.6	Co vor res fai
3	Female	2900	28	CVVHDF	24	1736	154	No	Yes	91.1	3.79	Po-fee vor res fai
4	Female	3200	25	CVVHDF	36	2540	198	No	Yes	92.2	2.56	Vo res fai
5	Female	2950	7	CVVHDF	36	2233	345	Filter blockage	No	84.5	2.34	Co vor
6	Male	3930	23	CVVHDF	36	3758	156	No	Yes	95.8	2.66	Re: fai
7	Female	3800	11	CVVHDF	48	4561	721	CVC revision	No	84.1	1.75	Co vor po
8	Male	3900	9	CVVHDF	36	3600	270	No	No	92.5	2.56	Po-fee vor
9	Male	3000	12	CVVHDF	48	3000	176	Hypothermia	Yes	94.1	1.96	Re: fai vor
10	Female	2750	13	CVVHDF	48	3767	20	Filter blockage	Yes	99.4	2.07	Re: fai vor
11	Female	3670	15	CVVHDF	24	2430	422	No	Yes	82.6	3.44	Re: fai fee
12	Male	3780	7	PD	48	2600	303	No	No	88.3	1.83	Po-fee vor
13	Female	2150	9	PD	72	2440	600	No	Yes	75.4	1.04	Po-fee res fai
14	Male	3600	10	PD	156	4667	675	No	Yes	85.5	0.54	Po-fee vor res fai
15	Male	2800	8	PD	135	3600	967	Blockage, revision	No	73.1	0.54	Po-fee vor coi
16	Male	3000	28	PD	120	4115	250	No	Yes	93.9	0.78	Po-fee vor res fai

CVC: Central venous catheter, CVVHDF: Continuous veno-venous hemodiafiltration, MV: Mechanical ventilation, PD: peritoneal dialysis, RRT: Renal replacement therapy.

Table 2
Comparison of means of continuous variables according to treatment modalities

Renal Replacement Therapy method							
	CVVHDF (n = 11)			PD (n = 5)			
	Mean Rank	Sum of Ranks	median(minimum-maximum)	Mean Rank	Sum of Ranks	median(minimum-maximum)	p*
Dialysis time (hour)	6.14	67.50	36 (12–48)	13.70	68.50	120(48–56)	0.01
Pretreatment plasma leucine levels (µmol/L)	7.86	86.50	3000 (1736–5796)	9.90	49.50	3600 (2440–4667)	0.42
Posttreatment plasma leucine levels (µmol/L)	7.00	77.00	198(20–721)	11.80	59.00	600(250–967)	0.08
Leucine reduction rate % achieved	9.73	107.00	91.7(82.6–99.4)	5.80	29.00	85.5(73.1–93.9)	0.12
Leucine reduction rate % per hour	11	10.91	2.56(1.75–7.6)	3.20	16.00	0.78(0.54–1.83)	0.001
*Mann whitney U test, CVVHDF: Continuous veno-venous hemodiafiltration, PD: Peritoneal dialysis.							

Figures

Figure 1

Leucine reduction rate % per hour

Figure 2

Posttreatment plasma leucine levels ($\mu\text{mol/L}$)

Figure 3

Dialysis time (hour)