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CASE SERIES

Continuous venovenous hemofiltration in neonates with hyperammonemia. A case series

Uso de Hemofiltración veno-venosa continua en neonatos con hiperamonemia. Serie clínica

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Abstract

Introduction: Neonatal hyperammonemia secondary due to inborn errors of metabolism is a rare condition with a high rate of neurological sequelae and mortality. Initial medical management is often insufficient to stop the progressive increase of ammonia, with the consequent deterioration of the patient. For this reason, depurative techniques have been implemented, including peritoneal dialysis, intermittent hemodialysis and continuous renal replacement therapy (CRRT). **Objective:** To describe our experience with continuous extracorporeal dialysis in severely ill neonates with hyperammonemia. **Patients and Methods:** Retrospective review of clinical records of neonates with hyperammonemia due to congenital errors of metabolism undergoing CRRT admitted in our institution in the last 6 years. Demographic data, chronological and gestational age, gender, anthropometric and laboratory data (creatininemia, ammonemia), and severity index PIM-II where collected. It was analyzed the CRRT: modality, duration and complications. The stard of therapy depended on the response to medical management in the first 24 hours, progressive neurological involvement, or increased blood ammonia (> 400 µg/dl) at the time of admission. CRRTs were performed using the Prisma Flex system and M100 and/or HF20 filters. **Results:** 6 neonates, 4 males, half of them with a history of prematurity, all with severe acute neurological involvement and severe ammonemias (> 1,000 µg/dl). The average age and weight at the start of the CRRT were 10 days and 2798 g, respectively, ammonia (median) 1,663 µg/dl (range 1,195 - 3,097). The PIM-II score had a median of 53 (range 13.4 - 87.4). On average, patients were 49.5 hours in continuous therapy. In four neonates, a mixed convective and diffusive technique (hemodiafiltration) was used, and only convective one (hemofiltration) in the 2 remaining. Mortality was 33%, and one of the survivors had permanent moderate neurological damage in clinical follow-up. **Conclusions:** The results obtained in this extremely ill group of neonates encourage us to propose this dialytic therapy as an excellent alternative in the management of this type of patients.

Keywords:
Hyperammonemia, neonates, inborn errors of metabolism, continuous renal replacement therapy

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Introduction

Neonatal hyperammonemia (NHA) is a serious condition that could be due to an inborn error of metabolism (IEM), mostly associated with defects of the urea cycle and organic acidemias[1]. Its prevalence is low (1:9,000 live births) and usually occurs in term newborns (NB), without dysmorphias, who quickly begin to show food rejection, lethargy, seizures and coma[1,2]. The early detection and an appropriate non-dialytic medical management of this condition can stabilize the clinical situation, preventing its progression to death, especially due to cerebral edema and irreversible neurological damage. Unfortunately, many of these patients are late diagnosed, with advanced neurological involvement and very high ammonia levels. An aggressive dialysis intervention, combined with baseline medical treatment in these patients had shown that it can decrease hyperammonemia more quickly and it can improve prognosis[1-4]. In theory, extracorporeal depurative techniques such as hemodialysis and continuous renal replacement therapy (CRRT) should be preferred over peritoneal dialysis (PD) since they achieve a significantly higher ammonium depuration rate[5], but these therapies present higher technical difficulties and the need of more resources in their implementation, especially in the case of severely ill newborns (NB)[2].

The objective of this study is to describe our experience in continuous extracorporeal dialysis in severely ill NB with NHA.

Patients y Method

The clinical cases of patients under 28 days of age hospitalized in our Pediatric Intensive Care Unit (PICU) diagnosed with NHA due to IEM were retrospectively assessed between 2010 and 2016, where a CRRT was used as a depurative method. The following data were obtained from each clinical record: demographic (age, gender, gestational age at birth), anthropometric (weight) and laboratory data (creatininemia, ammonemia). In addition, data were extracted from the CRRT used (modality, duration, complications). The beginning of this therapy depended on the criteria of the PICU team present at that time but basically guided by a response to medical management in the first 24 hours, progressive neurological involvement, or increased blood ammonium levels (> 400 µmol/L) at the time of admission.

The ammonia level was performed in the peripheral venous blood (1 ml) without a tourniquet and then the sample was sent to the laboratory in EDTA tube using cold packs. In order to determine the ammonia level, the enzymatic glutamate dehydrogenase method (Abbott, Architect) was used. It was considered hyperammonemia when the ammonia value in blood was > 200 µmol/L (280.2 µg/dl).

The Pediatric Index of Mortality II (PIM-II) was used as severity index.

Once the diagnosis of NHA was confirmed and in concomitance with dialysis therapy, all patients received medical therapy consisting of protein restriction, intravenous glucose and lipids, L-carnitine, L-arginine, hydroxocobalamin and biotin administration, and drugs that facilitate urinary ammonium excretion, such as benzoate and/or sodium phenylbutyrate. The CRRT were performed with the Prisma Flex system (Gambro Healthcare, Lakewood, CO, USA), which uses M100 and/or HF20 filters (Gambro Healthcare) with their respective integrated circuits. The priming of the extracorporeal circuit was performed with red blood cells from a blood bank, diluted in a solution of 5% albumin or normal saline to reach a hematocrit level between 30 to 40%. When replacement fluid was required, usually in the pre-filter inlet, or countercurrent dialysis, or both, Prismasol BGK 2/3.5 solution (Gambro Healthcare) was used, infused at an initial velocity (replenishment flow (Q_r), dialysis flow (Q_d) or $Q_r + Q_d$] of 2000-2500 ml/1.73 m^2/hour. Children were kept all the time in radiant cribs in order to avoid hypothermia (rectal temperature < 36°C). The vascular access routes were obtained with 1 lumen 3-4F Power Picc® catheters (Bard Access Systems, Inc., Utah, USA) and were placed by the pediatric intensivist or the interventional radiologist on duty. The initial blood flow velocity (Q_b) was between 8-20 ml/kg/min (minimum flow 30-50 ml/min). The net fluid removal rate (Q_{uf}) of each patient was defined according to the degree of volume overload and the clinical urgency of this removal. In addition, the initial CRRT modality that was used in each patient was established according to the clinical judgment of the intensivist on duty and it was changed (techniques with higher solute clearance and/or greater fluid ultrafiltration) according to the clinical need of the patient.

For anticoagulation, sodium heparin infused prefilter was used at a rate of 5-20 U/kg/hr after an initial bolus of 10 U/kg. Subsequently, the infusion rate of heparin was adjusted to maintain the activated clotting time (Hemochron® Response, International Technidyne Corp., NJ, USA) between 180 and 200 seconds.

The decision of disconnection of CRRT was recorded as an improvement of their clinical condition (correction of the cause that justified the dialysis), death, suspension for ethical/clinical reasons, or change to another dialysis therapy.

This study was approved by the Research Ethics Committee of the School of Medicine of Clínica Alemana-Universidad del Desarrollo.

Table 1. Patients with neonatal hyperammonemia treated with CRRT

Patient N°	1	2	3	4	5	6
Gender (M/F)	M	M	F	M	F	M
Age at admission (days)	23	3	6	5	6	17
Admission weight (gr)	2480	3030	3000	2470	2750	3060
Metabolic diagnosis	Propionic acidemia	Methylmalonic acidemia	Argininosuccinic acidemia	OTC deficiency	Propionic acidemia	OTC deficiency
Ammonemia at admission (ug/dL)	3097	1350	1195	1466	2662	1860
CRRT used	CVVH	CVVH	CVVHDF	CVVHDF	CVVHDF	CVVHDF
Vascular acceses	FV/ IJV	FV/SCV	FV/IJV	UV/AxA	FV/FV	FV/FV
Survival	(+)	(+)	(-)	(+)	(-)	(+)
Gestational age (weeks)	35	38	39	35	36	38
CRRT duration (hours)	57	74	24	96	24	22

AxA: axilar artery, CVVHDF: continuous venovenous hemodiafiltration, CVVH: continuous veno-venous hemofiltration, OTC: ornithine transcarbamylase, CRRT: continuous renal replacemenr therapy, FV: femoral vein, SCV: subclavian vein, UV: umbilical vein, IJV: internal jugular vein.

Results

In the assessed period, there were six neonates with IEM and NHA that underwent CRRT (table 1). Two thirds (4/6) of the patients were male and half of them (3/6) had a gestational age at birth < 37 weeks. The average age and weight at the time of starting dialysis therapy was 10 days and 2,798 gr, respectively, with an average ammonia value of 1663 µg/dl with a range of 1,195 to 3,097 µg/dl (normal value: 31-123 µg/dl). The PIM-II of these patients had an average of 53, with a range of 13.4 to 87.4. The etiology of NHA could be identified in all patients, and they were mainly organic acidemias. On average, patients were in continuous therapy during 49.5 hours, and only in one case it was necessary to continue with PD for 48 more hours due to difficulty in controlling hyperammonemia with medical therapy. Regarding the selected CRRT, a mixed convective and diffusive dialysis technique (hemodiafiltration) were used in four neonates, and only a convective one (hemofiltration) was used in the remaining two. One third (2/6) of the patients died: one patient died of refractory cerebral edema on the 10th day of hospitalization, despite achieving ammonium levels < 300 µg/dl (214.2 µmol/L) in less than 12 hours, and the other patient died at 44 hours after admission to PICU, due to septic shock of enteral origin (necrotizing enterocolitis) and multiple organ failure. Among the survivors, in a follow-up period of 2.3 years on average, only one patient remains with neurological damage, and the other three have no evidence of psychomotor developmental delay until the present time.

Discussion

The medical emergency of NHA requires quick action. Ammonium is a potent neurotoxin and can cause an irreversible neurological damage when its blood concentration exceeds 800 µmol/L (1,129.6 µg/dl) for more than 24 hours[6]. In some patients, pharmacological therapy by itself does not produce a quick decrease in ammonium levels which are needed to prevent permanent neurological damage, thus it is necessary to start RRT as soon as possible when ammonium levels are > 400 µmol/L (560.3 µg/dl), with the objective of reducing them to < 200 µmol/L (280.2 µg/dl) in the shortest time possible[7]. In relation to dialysis therapies, it is known that the ability to remove a toxin is not only a function of the calculated clearance rate, it also depends on the distribution volume, the molecular weight and the degree of protein binding of that substance[3]. Due to these physiological characteristics, in the case of hyperammonemia, "rebounds" of their plasma concentration usually occur when the RRT is not maintained over time.

The NHA is the most common indication for renal replacement therapy in NB without acute renal failure[3,7]. Since PD is depuratively less efficient than vascular techniques, it would not be the first-line alternative in situations of blood accumulation in the "dangerous" range of an exogenous or endogenous toxic substance, unless there was no other alternative available[2,8,9]. Intermittent hemodialysis offers the most efficient and fastest way to remove ammonia from the blood, but it is technically complex to perform in young children

because of the hemodynamic instability it produces, in addition to a rapid rebound of ammonia when it stops[7,10].

In our clinical series, patients showed variable neurological involvement and very high blood ammonium levels at admission. Their mortality (33%) was similar to other centers (2, 3.5) and did not correlate with the ammonemia value at the time of connection to CRRT. In this regard, Westrope et al. observed that in a group of 14 neonates with hyperammonaemia undergoing CRRT, with a 64% global survival, the average pre-dialysis ammonia level of the survivors was 638 µg/L versus 1057 µg/L in those who died[11]. In relation to the CRRT technique used in our group, it is not different from what is traditionally used in reported cases of neonates with severe renal failure[7,11-,13]. In this sense, a recent publication suggests that these CRRT in NHA could have even better outcomes using higher doses of dialysis/replacement solution (8000 versus 2000 ml/h/1.73 m^2), which would reduce the ammonium values in less time[14].

In the analysis of the CRRT modalities applied to these patients (hemofiltration versus hemodiafiltration), there was no significant difference in survival results. There is no published evidence in the literature that diffusive techniques are objectively better than convective ones in NHA management.

This study has some limitations. First, it is a clinical series with a small number of patients included, which does not allow to generalize conclusions. Second, since it is a retrospective study, the treating physicians did not record the data in the clinical record according to a protocol, therefore it was not always complete, especially in those cases in which the patients were transferred from another health care center (50%) for dialysis therapy. For the same reason, the clinical management of these patients was not necessarily equal.

Despite these deficiencies, we believe that the objective of demonstrating that CRRT is an useful and efficient procedure in the management of NHA in our field is achieved.

Conclusion

Our experience with CRRT for the treatment of patients with NHA due to IEM, in which the quick neurological damage caused by this condition is known, has been successful in increasing the survival of these children, achieving it with neurological indemnity, similar to experiences of other foreign centers. We suggest an early implementation of this therapy in neonatal intensive care units that treat patients with NHA in whom medical therapy fails to control the increase of ammonium levels in blood or in which a progressive deterioration of the neurological examination is observed.

Ethical responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Financial Disclosure

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Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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