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Continuous Renal Replacement Therapy for Hyperammonemia caused by Ornithine Transcarbamylase Deficiency

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Abstract

Ornithine transcarbamylase (OTC) deficiency is one of the most severe inborn errors of metabolism that causes hyperammonemia.[1)] At the end of 1995, the 5-year survival rate for patients with neonatal-onset OTC deficiency was 22%.[2)] By 2011, the 1-year survival rate for patients with neonatal-onset OTC deficiency was 90% (69/77). [3)] For managing hyperammonemia, it is crucial to rapidly decrease ammonia levels. Although continuous renal replacement therapy (CRRT) is widely used in newborns with hyperammonemia induced OTC deficiency, the method is not standardized, and there is lack of newborn-specific equipment. We perform aggressive CRRT in the neonatal intensive care unit (NICU) using continuous veno-venous hemodiafiltration to manage hyperammonemia caused by OTC deficiency.

Methods

We performed CRRT as follows:

- For vascular access, a 6-Fr catheter was inserted into the right internal jugular vein by the cut-down or puncture method. This access allowed the maintenance of an appropriate blood flow rate.
- The circuit was primed with blood that was previously dialyzed to decrease the potassium level.
- For high efficiency, we selected a purification membrane ≥0.3 m^2 and combined peritoneal dialysis.
- A catecholamine was administered before beginning CRRT. This prevents a decrease in myocardial contractile force, as observed on echocardiography, which in turn prevents an initial drop in blood pressure.
- To prevent complications such as intracranial or gastrointestinal bleeding, we discontinued CRRT as soon as the ammonia level decreases to ≤300 μg/dL.

Results

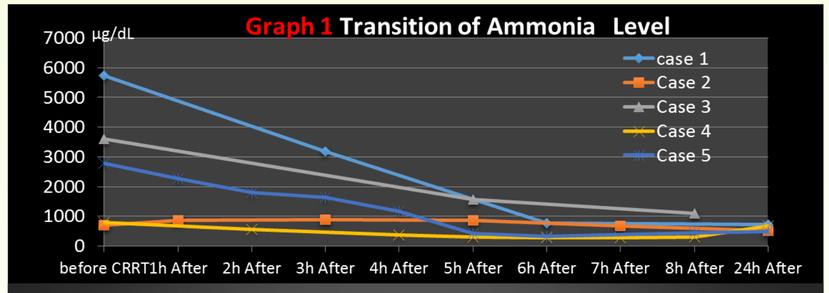
CRRT was used to treat hyperammonemia caused by OTC deficiency in 5 cases in our NICU; the mortality rate was 40% (Patients 1 and 3). We did not observe any complications. The average CRRT time was 20 h (range, 5–49 h). In 1 case, CRRT was restarted because the ammonia level increased to >400 μg/dL (Patient 1). However, dialysis efficiency was adequate because ammonia levels stabilized without restarting CRRT in the 3 surviving patients. As to the clinical course of the 3 survivors, 1 patient later died before living-related donor liver transplantation, while the remaining 2 patients successfully underwent liver transplantation. However, mild psychomotor retardation was observed in the 2 survivors after liver transplantation.

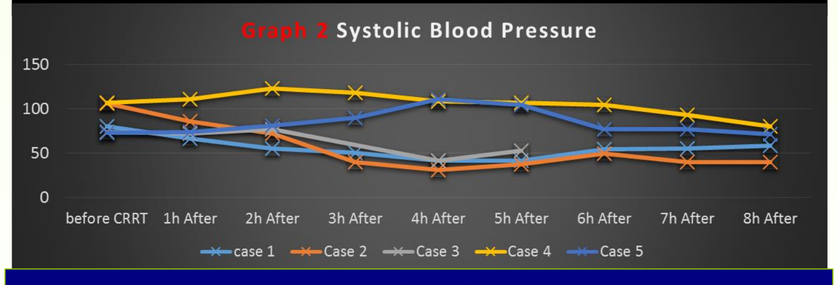
Case #	1	2	3	4	5
Onset (Days of Life)	2	3	2	6	2
Birth Weight	3345g	3424g	3000g	3300g	3182g
Major Complaint	Shivering of Right Arm	Convulsion	Limbs Stiffening Irritability	Lethargy Hypothermia	Hypothermia
NH_3 levels on the admission	733 μg/dL	715 μg/dL	1608 μg/dL	806 μg/dL	526 μg/dL
Maximam NH_3 Level	5730 μg/dL	871 μg/dL	3610 μg/dL	806 μg/dL	2780 μg/dL
Time to Initiation of CRRT (from admission)	22h	16h	4h	6h	7h
Blood Flow (ml/min)	19 (5.7ml/kg/min)	14 (4.1ml/kg/min)	15 (5.0ml/kg/min)	19 (5.8ml/kg/min)	22 (6.9ml/kg/min)
Dialysate Flow (ml/min)	5～20	25～28	2.5～5.8	3.3～21.7	20～40
Initial Drop	None	None	None	None	None
Time of Liver Transplant	None	None	None	1y. 4m.o.	9m.o.
Outcome	Dead of 16	Discharge of 44	Dead of 3 (During CRRT)	Discharge of 36	Discharge of 41

Discussion

Neonatal hyperammonemia is treated by decreasing ammonia levels to prevent neurological damage. Our method of CRRT for newborns can significantly decrease ammonia levels within 24 h. (Graph 1) By priming blood and concomitantly administering a catecholamine infusion, an initial drop in blood pressure was prevented. (Graph 2) Ammonia level was significantly higher in the 2 patients (Patients 1 and 3) who died than in those who survived, implying that Patient 1 died because of a rapid increase in ammonia level due to the complete absence of the OTC gene region and delayed initiation of CRRT. Patient 3 died because of significantly high ammonia level on admission that led to circulatory failure.

Based on our experience, it is important to start CRRT in cases of hyperammonemia where ammonia levels are >400 μg/dL. Moreover, as the 2 survivors have neurological sequelae probably due to prolonged hyperammonemia, we consider it necessary to reduce the ammonia level as quickly as possible without causing complications such as hypotension or electrolyte imbalance. Dialysis efficiency can be increased maximally when the dialysate flow rate is increased twice the blood flow rate. Dialysis efficiency is dependent on the membrane surface area, the blood flow rate, and the dialysate flow rate. The extent to which the membrane surface area can be widened is limited because of a limited priming volume in newborns. Vascular access for ensuring blood flow should be carefully selected in order to maximize dialysis efficiency. Our combined method of peritoneal dialysis helps reduce the ammonia level in a short time and seems useful for preventing increases in ammonia levels after CRRT.





Conclusions

Our CRRT method could effectively reduce ammonia level in neonates with hyperammonemia caused by OTC deficiency.

References

1. Snyderman SE. Clinical aspects od disorders of the urea cycle. Pediatrics 1981;68:248-9,295-7
2. Uchino T. Et al. Neurodevelopmental outcome of long-term therapy of urea cycle disorders in Japan. J Inherit Metab Dis. 1998;21 Suppl 1:151-9.
3. Kido J. et al. Long-term outcome and intervention of urea cycle disorders in Japan. J Inherit Metab Dis. 2012 35:777-785