Sapporo Medical Journal
Volume 54, Issue 10, October 2020

Application of Continuous Renal Replacement Therapy for Severe Hand, Food and Mouth Disease: A Serial Case Study

Ha Manh Tuan[1], Do Chau Viet[2], Nguyen Tuan Anh[3]

[1] University of Medicine and Pharmacy at Ho Chi Minh city, Vietnam.
[2] Children's Hospital 2, Ho Chi Minh city, Vietnam
[3] Molecular Biomedical Center, University Medical Center - Campus 2, Ho Chi Minh City, Vietnam

Abstract— Despite the continuous renal replacement therapy (CRRT) indicated on patients with severe (Grade 4) hand, foot and mouth disease (HFMD), the mortality rate is high.The aim of the study was to assess the effectiveness of CRRT in earlier stages of severe HFMD pediatric patients on improving their mortality.A retrospective, case series study was conducted on severe HFMD cases diagnosed clinically, confirmed by polymerase chain reaction (PCR) assay and received CRRT. Variables were recorded at:Pediatric intensive care unit (PICU) admission, CRRT initiation and 16 hours after CRRT intervention. Data were processed and analyzed using STATA version 14.0. Thirty-eight eligible cases were included in the study. The mean age was 25.3 months; the male:female ratio was 1.5. Most cases were admitted within the first 3 day of illness (94.7%). The rate of HFMD grade 3 and grade 4 indicated CRRT was about 26.3% and 73.7% respectively. Vital signs, hematological and biochemical parameters improved significantly after 16 hours of CRRT. The average duration of CRRT was 2.4 ± 0.7 days. The survival rate of cases with HFMD grade 3 was 82.1% higher than that of cases with HFMD grade 4 at 40% significantly. The overall survival rate of HFMD patients indicated CRRT was about 71%.The CRRT could be considered as one of the measures contributing to the improvement of mortality rate in patients with severe HFMD.Early indication of CRRT can greatly improve clinical outcome in severe HFMD patients.

Keywords: Enterovirus A71, hand foot mouth disease, continuous renal replacement therapy.

INTRODUCTION

Hand, footand mouth disease (HFMD) is an infectious disease which is transmitted via fecal – oral route. This disease is caused by enteroviruses, of which,*Coxsackie A16* and *Enterovirus A71* (EV A71) are the most frequently encountered[1, 2]. HFMD occurs in many places around the world, but more popular in Western Pacific and Asian regions, and can turn into large outbreaks[2].HFMD is one of three most common types of infectious diseases(together with Dengue hemorrhagic fever and encephalitis)among Vietnamese children. In Viet Nam, the prevalence of HFMD ranges from 100.000 to 130.000 cases annually. The first outbreak of HFMD was reported in 2003 in Ho Chi Minh city [3]. There were 174,677 cases with 200 deaths recorded between 2011-2012[4]. EV-A71 is significantly associated with severe illness[5] and causes a substantial economic burden in Vietnam [6].The disease is commonly diagnosed in children with the age of 1 – 3 years and can lead to death if severe complications are not managed appropriately[1, 2, 7].

HFMD is classified into 4 grades based on its severity[8]. HFMD grade 1 consists of fever and skin lesions with or without oral lesions. HFMD grade 2 is with one of the followings: myoclonic jerk, tremor, ataxia, limb weakness or lethargy. HFMD grade 3 is complicated with autonomous nervous system (ANS) dysregulation. HFMD grade 4 is HFMD grade 3 with any of the following symptoms: hypotension, pulmonary edema or heart failure. Patients with grade 1 and grade 2 (uncomplicated) HFMD are supportively managed. Provided thatsigns of central nervous system involvement present, patients are closely monitored. Patients with HFMD grade 3 are monitored in intensive care unit and indicated with intravenous immunoglobulin (IVIG), dobutamine, and milrinone. Patients with HFMD grade 4 are supported by ventilator and vasoactive drugs, infused with IVIG and indicated with continuous renal replacement therapy (CRRT).

So far, there have been few studies reporting the application of CRRT for patients with HFMD grade 4[9, 10]. The preliminary results from application of CRRT for patients with HFMD grade 4 were encouraging although the mortality rate was still high[9].In the present study, we conducted a serial

case study to evaluate the effect of CRRT on improving clinical signs and laboratory measurements in earlier stage of the severe HFMD pediatric patients.

METHOD

Study design

We set up a retrospective serial case study of severe HFMD pediatric patients with cardiopulmonary complications caused by EV-A71. The study was approved by the Institutional Review Board (IRB) of Children's Hospital 2 - Ho Chi Minh City. The informed consent form was waived, as we use unidentified retrospective data.

Patients

1207 pediatric patients with HFMD were diagnosed during the survey period, according to guidelines of Vietnamese Ministry of Health [8]. 270 cases were of severe HFMD. Thirty-eight severe HFMD patients admitted to the Infectious Diseases Ward, Children's Hospital 2 from 2011-2015 and received CRRT were eligible and accepted into the study.

The inclusion criteria were as follow:(1) less than 15 years old; (2) patients with severe HFMD grade 3 and 4; (3) HFMD cases positive with EV-A71 confirmed by real time RT-PCR. Patients were excluded if they had one of the following conditions: (1) Patients with associated diseases; (2) patients with missing data in medical records.

Patients'intervention

Patients were classified as grade 3 and 4 according to Vietnamese Ministry of Health guidelines as described above. All cases were treated in accordance to the mentioned guidelines. EV-A71 positive cases were confirmed by real time RT-PCR. The conventional treatments include immunoglobulin 1g/kg/dose (the second dose could be considered based on patient's condition); phenobarbital 10-20 μg/kg in 30 minutes, milrinone 0.4 μg/kg/min in up to 72 hours; dobutamine 5 μg/kg/min to maximum 20 μg/kg/min; mechanical ventilator and normal saline or lactate ringer 5ml/kg/15 minutesin patients with shock. If patients were suspected to have nosocomial infection or sepsis, appropriated antibiotics were given.

Patients with HFMD grade 3 were treated with the abovementioned conventional therapy and monitored every 1 hour in the intensive care unit. If the patients did not improve after 24 hours of conventional treatment, CRRT would be indicated. Patients with HFMD grade 4 on admission or deteriorating into HFMD grade 4 during close monitoring in the intensive care unit would be indicated for CRRT.

All therapeutic decisions were made independently by the attending practitioners according to standard practice in intensive care unit.

CRRT procedures

The CRRT was carried out with Prismaflex machine(Baxter, America), and M60 – M100hemofilter membrane, substitution fluid Hemosol. Vascular access was done with double lumen 6.5 – 8 F central venous catheter(Vygon, France) in the right internal jugular or femoral vein, according to patient's body weight.Continuous venous – venous hemofiltration (CVVH) mode was chosen. The rate of infusion pump averaged 5 ml/kg/min. The ratio of the pre- to post-dilution was 1:2. The filter circuit was pretreated with saline containing unfractionated heparin. During CVVH, heparin was used with an infusion of average 15 UI/kg/h. The activated partial thromboplastin time (APTT) was tested every 8 hours. The hemofilter was changed every 24 hours, or when transmembranepressure greater than 200 mmHg, or when clotted. The indications, performance, and management for CRRT maintained uniform standards in our study.

Data collection

Data from eligible cases was obtained from hospital records and entered to an electronic database, using standard case report form (CRF). Key variables were defined prior to data collection, included demographic data, clinical signs, vital signs, severity of disease, indication of CRRT, laboratory parameters such as biochemical indexes, liver and kidney function tests, cardiac enzymes, electrolytes, coagulation, glycaemia and patient's outcome.The variables were recorded at admission, at the beginning of CRRT, and every 8 hours after CRRT application.All data were collected in well-designed case report forms.

Statistical analysis

Continuous and categoricalvariables were described by means ± SDs and percentages, respectively. All variables were tested for normal distribution by using the Kolmogorov-Smirnov test. Independent-sample *t*test was used to compare parameters in different groups. Chi-square tests were applied to compare two percentages. All tests were two sides, and *p* values that were less than 0.05 were considered to be statistically significant. All statistical analyses were performed with the STATA software version 14.0.

RESULTS

Demographic characteristics of patients

There were 38 eligible patients enrolling in the study during the period of 4 years from 6/2011 – 12/2015. Among these patients, the mean age was 25.3 months (11 – 128 months) with 86.6% of cases reported in children younger than 3 years old. The male:female ratio was 1.5. The majority of patients (73.6%) lived in Ho Chi Minh (HCM) city and neighboring provinces, such as Binh Duong and Dong Nai. 100 % of these cases were infected with *Enterovirus A71*, which was confirmed by real-time PCR methodfrom at least one sample either throat swabs or rectal swabs. 87% of rectal swabs and 92% of throat swabs werepositive with*Enterovirus A71* (Table 1). Of 38 severe HFMD patients prescribed CRRT, 11 patients died, and the overall hospital mortality was 1% (mortality rate in severe cases was 4%).

Table 1. Demographic characteristics and CRRT indications

	Number of cases	Rate(%)
Gender		
Male	23	60.5
Female	15	39.5
Age (months)	25.3 ± 8.2	
Residency		
Ho Chi Minh city	11	28.9
Binh Duong	11	28.9
Dong Nai	6	15.8
Others	10	26.4
Sources of transmission		
Kindergarten	16	42.1
Home	22	57.9
Length of illness < 3 days before admission	36	94.7
Enterovirus A71 confirmed	38	100
Indication of continuous renal replacement therapy		
Grade 4	10	26.3
Grade 3	28	73.7
Diminished consciousness	10	26.3
ANS* dysregulation	11	28.9
Abnormal breathing	7	18.4

* ANS: autonomous nervous system

The rate of cases with HFMD grade 4 with CRRT indication was only 26.3% (10/38), around three times lower than the rate of cases with HFMD grade 3 having CRRT, 73.7% (28/38). Indications of CRRT for the grade 3 HFMD patients included depressed consciousness (26.3%, 10/38), ANS dysregulation (28.9%, 11/38), and abnormal breathing (18.4%, 7/38) (Table 1).

Effectiveness of continuous renal replacement therapy

The vital signs of severe HFMD patients improved significantly 16 hours after the initiation of CRRT (table 2). Patients' temperature was about 38.8°C at admission, rose over 39°C when their conditions worsened and remained high until starting CRRT. Patients' temperature declined about 1°C / 4 hours after initiation of CRRT, dropped gradually and became stable at the twelfth hour of CRRT (Figure 1). Patients' mean pulse reached a peak of 180 ppm at the beginning of CRRT, it decreased by 10 ppm correlating with the drop of 1°C in the mean temperature at the fourth hour of CRRT, then maintained 150 ppm at the sixteenth hour (Figure 1). In terms of mean systolic arterial pressure, it declined 10 mmHg / 2 hours after the CRRT was initiated, then returned to normal at the eighth hour of CRRT and became stable at the sixteenth hour (Figure 1).Similarly, the laboratory results showed better changes 16 hours after the initiation of CRRT. The serum glucose, troponin, creatinine, CRP, ALT level improved significantly at the sixteenth hour of CRRT (Table 2).

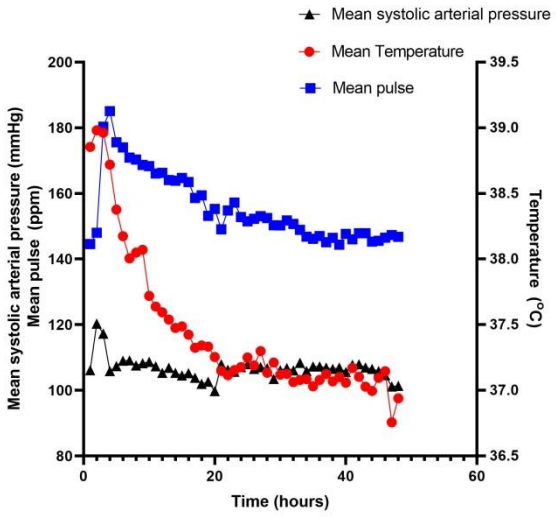

Fig. 1 Changes in patients' mean temperature, mean pulse and mean systolic arterial pressure during the course of CRRT

Table 2. Changes in vital signs and laboratory results between starting continuous renal replacement therapy and 16 hours later

CRRT time point	**0 hour**	**16 hours**	P(t-test)
Vital signs			
Pulse (ppm)	180.3 ± 27.5	159.2 ± 26.3	<0.05
Temperature (°C)	39.0 ± 1.1	37.5 ± 1.0	<0.05
Systolic blood pressure (mmHg)	120.0 ± 28.0	109.2 ± 24.1	<0.05
Laboratory parameters			
WBC[4] (x 1000 / mm^3)	16.1 ± 6.8	12.1 ± 4.2	<0.05
Platelet count (x 1000 / mm^3)	382.6 ± 114.0	189.7 ± 60.9	<0.05
Hemoglobin (g/l)	11.0 ± 1.6	9.6 ± 1.7	>0.05
Glycemia (mg/l)	150.0 ± 88.5	133.6 ± 74.0	<0.05
Troponin I (ng/ml)	3.9 ± 3.9	2.7 ± 2.8	<0.05
Venous lactate (mmol/l)	2.2 ± 1.3	2.0 ± 0.7	>0.05
Creatinine (mg/l)	5.6 ± 2.4	4.1 ± 1.3	<0.05
CRP[1] (mg/l)	15.2 ± 23.0	8.5 ± 5.9	<0.05
AST[2] (U/l)	66.2 ± 44.1	62.7 ± 42.0	>0.05

ALT[3] (U/l)	27.0 ± 16.9	17.0 ± 3.6	<0.05

[1]CRP: C-reactive protein; [2]AST: Aspartate aminotransferase; [3]ALT: Alanine aminotransferase; [4]WBC: White Blood Cell.

Outcome of continuous renal replacement therapy

The mean duration of CRRT was 2.4 ± 0.7 days. It was 2.8 ± 0.4 days for survivors. The rate of survivors in grade 3 HFMD patients was twice of that in grade 4 HFMD patients (p=0.015, $\chi 2$ test) (Table 3).

Table 3. Outcome of continuous renal replacement therapy for severe HFMD patients

	Number of cases	Survivor	Rate of survivor (%)
Grade 3	28	23	82.1
Grade 4	10	4	40.0
Total	38	27	71.0

DISCUSSION

Thirty-eight cases of severe HFMD were enrolled. Most of them were under 3 years old and admitted within the first 3 day of illness. The morbidity was higher in male than in female. Enteroviruses were confirmed by real-time PCR techniqueusing either throat swabs or rectal swabs. Our data showed that the severe HFMD cases were commonly caused by *Enterovirus 71*, mainly occurring in young children and progressed rapidly within the first few days of illness. These were in agreement with many previous studies[1, 7, 9].

According to a guideline developed byVietnameseMinistry of Health in 2011[8], the HFMD cases are classified as grade 4 when the patientpresents one of the following conditions: shock, pulmonary edema, central cyanosis or grasping breathing, whereas the HFMD cases grade 3 include signs of ANSdysregulation such as tachycardia at 150-170 ppm, hypertension, profuse sweating and respiratory abnormalities (tachypnea or difficulty with breathing). The CRRT is only indicated for severe HFMD patients with grade 4;meanwhile HFMD cases with grade 3 have not yet been recommended for CRRT. However, we have realized that if the CRRT is initiated for patients with HFMD grade 4, the mortality rate will be substantially high; whereas the outcome will be more desirable if the CRRT is indicated early for grade 3 HFMP patients who have presented with the signs of ANSdysregulation. From our clinical observation, we apply the CRRT to grade 3 HFMD cases who did not respond well to treatments following the guideline[7], so the use of CRRT for severe HFMD cases grade 3 was much higher than that for severe HFMD cases grade 4 in this study. The overall survival rate of severe HFMD cases with CRRT indication is significantly higher in our study than in Tien's study[9]. In this study, the author indicated CRRT mainly for severe HFMD patients grade 4 (90%) and the mortality rate was twice as higher, compared to our study.

This study has shown the manifestation of ANS dysregulation such as high fever, tachypnea, arterial hypertension improved remarkably at 16 hours after CRRT initiation. Similarly, laboratory abnormalities normalized after 16 hours of CRRT. All cases with pulmonary edema ameliorated at the same time. The mechanism of CRRT resulting in a favorable outcome in the severe HFMD patients remained unclear. Although the effect of CRRT for patients with multiple organ failure caused by sepsis has been verified through the capacity of CRRT to remove mediators, recent studies have shown that in HFMD patients, fulminant clinical manifestations have probably been associated with the production of inflammatory cytokines and chemokines caused by EV 71 infection[11-14]. The fact that the CRRT can remove inflammatory mediators from blood by a convective mechanism and/or by adsorption to the membrane of the hemofilter may be an explanation for the effectiveness of CRRT in the management of severe HFMD patients[15, 16].

Beside the appropriate indication of CRRT for the severe HFMD patients, other factors have might contributed to the effectiveness of CRRT in management of the severe HFMD cases. They are that the medical equipment is always available, skilled staffs are ready to carry out the CRRT at any time.The preparation for performing CRRT must be rapid to gain valuable time to save the patients who

deteriorate rapidly.And last,providers' competency is requiredto deal with complications of severe HFMD and problems occurring during implementing CRRT.

Our study has several limitations. First, the number of pediatric patients enrolled in the study was small, so it might not be representative for the whole population. Second, the study designwas based on a retrospective serial case study without a control group,affecting the power of the conclusion. However, the strength of our study was that it was one of the first reports on applying CRRT for pediatric patients with early stage of severe HFMD from Vietnam. This study provided evidences for the application of CRRT in reducing the mortality rate in severe HFMD cases in Vietnamese pediatric patients.

CONCLUSION

This study has shown the effectiveness of CRRT in improving clinical signs and laboratory measurements in the HFMD patients with fulminant complications. The CRRT may be considered as a measure contributing to improve the outcome of the severe HFMD patients. Better outcomewas observed when CRRT was indicated early in severe HFMD patients grade 3 who do not respond well to appropriate treatments. However, the early indication of CRRT for severe HFMD patientsrequires further studies.

REFERENCES

1. Sun, L.M., et al., *An enterovirus 71 epidemic in Guangdong Province of China, 2008: epidemiological, clinical, and virogenic manifestations.* Jpn J Infect Dis, 2011. **64**(1): p. 13-8.
2. Organization, W.H., *A guide to clinical management and public health response for hand, foot and mouth (HFMD).*http://www.wpro.who.int/publications/docs/ Guidance for the clinical management of HFMD.pdf (access on 20.12.2017), 2011.
3. Manila, W.H.O., *A guide to clinical management and public health response for hand, foot and mount disease (HFMD).* 2011.
4. Khanh, T.H., et al., *Enterovirus 71-associated hand, foot, and mouth disease, Southern Vietnam, 2011.* Emerg Infect Dis, 2012. **18**(12): p. 2002-5.
5. Hoang, M.T.V., et al., *Clinical and aetiological study of hand, foot and mouth disease in southern Vietnam, 2013-2015: Inpatients and outpatients.* Int J Infect Dis, 2019. **80**: p. 1-9.
6. Nhan, L.N.T., et al., *Economic Burden Attributed to Children Presenting to Hospitals With Hand, Foot, and Mouth Disease in Vietnam.* Open Forum Infect Dis, 2019. **6**(7).
7. Kim, K.H., *Enterovirus 71 infection: An experience in Korea, 2009.* Korean J Pediatr, 2010. **53**(5): p. 616-22.
8. *A Guideline for Diagnosis and Treatment of Hand Foot Mouth Disease.* Ministry of Health, Viet Nam, 2011.
9. Tien, N.M., P.V. Quang, and T.H. Ut, *Factors related to the outcome of continuous renal replacement therapy for hand foot mouth disease with severe complications.* Journal of Medicine HCM city, 2014. **12**: p. 98-106.
10. Phan, P.H., et al., *Continuous veno-venous hemofiltration for treatment of enterovirus 71-induced fulminant cardiopulmonary failure: a case report.* J Med Case Rep, 2012. **6**: p. 159.
11. Lin, T.Y., et al., *Proinflammatory cytokine reactions in enterovirus 71 infections of the central nervous system.* Clin Infect Dis, 2003. **36**(3): p. 269-74.
12. Wang, S.M., H.Y. Lei, and C.C. Liu, *Cytokine immunopathogenesis of enterovirus 71 brain stem encephalitis.* Clin Dev Immunol, 2012. **2012**: p. 876241.
13. Wang, S.M., et al., *Pathogenesis of enterovirus 71 brainstem encephalitis in pediatric patients: roles of cytokines and cellular immune activation in patients with pulmonary edema.* J Infect Dis, 2003. **188**(4): p. 564-70.
14. Wang, S.M., et al., *Acute chemokine response in the blood and cerebrospinal fluid of children with enterovirus 71-associated brainstem encephalitis.* J Infect Dis, 2008. **198**(7): p. 1002-6.
15. Goldstein, S.L., et al., *Pediatric patients with multi-organ dysfunction syndrome receiving continuous renal replacement therapy.* Kidney Int, 2005. **67**(2): p. 653-8.

16. Peng, Z., et al., *The impacts of continuous veno-venous hemofiltration on plasma cytokines and monocyte human leukocyte antigen-DR expression in septic patients.* Cytokine, 2010. **50**(2): p. 186-91.