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Original Article

Clinical analysis of continuous blood purification for the treatment of children with fulminant myocarditis

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Abstract: In this study, we aimed to investigate the clinical value of continuous blood purification (CBP) for the treatment of children with fulminant myocarditis (FM). Forty-seven children with FM were recruited from the Department of Pediatric Intensive Care Unit of our hospital from November 2011 to April 2015, and were divided into an intervention group (children who underwent CBP) and a control group (children with no intervention). The following data were compared: sex; age; clinical outcomes; vital signs; and results of electrocardiogram (ECG), chest radiography, echocardiogram, and laboratory examinations. The differences in age and sex between the two groups were not statistically significant (P>0.05). The mortality of the intervention group (16.13%) was lower than that of the control group (43.75%), and the length of stay of the intervention group was shorter than that of the control group (P<0.01). After the treatment, the heart rate and blood pressure of the children in both groups improved to varying degrees. Abnormalities on ECG showed improvement, the cardio-thoracic ratio decreased, and impaired ejection fraction was restored. The laboratory examination results were all improved. The myocardial enzyme pattern and N-terminal pro-B-type natriuretic peptide (NT-proBNP) improved after 72 h in the control group and after 48 h in the intervention group. The levels of myoglobin, MB isoenzyme of creatine kinase, NT-proBNP, and lactic acid all significantly improved in the intervention group (P<0.01). We conclude that CBP could improve the outcomes in children with FM.

Keywords: FM, pediatric critical illness, CBP

Introduction

Fulminant myocarditis (FM) is a severe manifestation of viral myocarditis with acute onset and rapid progression. Congestive heart failure, cardiogenic shock, and other severe hemodynamic disorders may occur in the short term, and the mortality rate is extremely high [1]. Recently, many medical institutions proposed that providing treatment with mechanical circulatory assistance in vitro in the early course of the disease could effectively reduce the burden on the heart and improve circulation, allowing more time for basic medication to take effect [2-7]. However, relatively few studies have reported on the use of extracorporeal membrane oxygenation (ECMO) for the treatment of FM in children. Because of the technical challenges, high cost, and other factors, ECMO has not been widely used in the field of pediatric critical care. Moreover, left ventricular assist devices and percutaneous cardiopulmonary support systems are also rarely used in children because of their operational limitations. Given the high mortality rate of FM, it is important to develop a relatively safe, economical, and practical method of treatment for pediatric critical care patients. Given the therapeutic focus that early stabilization of hemodynamics and removal of inflammatory mediators can reduce immune damage [8], CBP was applied to the treatment of children with FM in this study. The aim of this study was to investigate the clinical therapeutic effect of CBP in children with FM.

Methods

General data

Forty-seven children with FM who met the exclusion criteria were recruited from the Department of Pediatric Intensive Care Unit of the First Hospital of Jilin University, during November 2011 to April 2015. The patients included 27 boys and 20 girls (sex ratio, 1.35:1). The range

Table 1. General data of children with FM

Index	Indicators
Cases	47
Females (cases/%)	27 (57.45)
Males (cases/%)	20 (42.55)
Age (month)	14.35 (8.00, 32.50)
Weight (kg)	12.70 (6.70, 15.75)
Course before admission (d)	2.55±1.54
Prodrome (cases/%)	
Respiratory symptoms such as cough, wheezing	21 (44.68)
Gastrointestinal symptoms such as nausea, vomiting	13 (27.66)
Neurological symptoms such as malaise, crying	10 (21.28)
Cardiovascular symptoms such as palpitation, chest tightness	3 (6.38)
Clinical symptoms and signs (cases/%)	
Shortness of breath	39 (82.98)
Dense small pulmonary rales	36 (76.59)
Interrupted apnea	2 (4.25)
Weakening pulse	38 (80.85)
Heart sounds low and blunt	35 (74.47)
Gallop rhythm	8 (17.02)
Pathologic murmur	12 (25.53)
Sychnosphygmia	38 (80.85)
Bradycardia	9 (19.15)
Hepatosplenomegaly	33 (70.21)
Cardiac shock	7 (14.89)
Changes of ECG (cases/%)	
Sinus tachycardia	33 (70.21)
Ventricular arrhythmia	5 (10.63)
First degree A-V block	5 (10.63)
Second degree A-V block	4 (8.51)
Third degree A-V block	2 (4.25)
Raised ST-T	4 (8.51)
Shifted down ST-T	3 (6.38)
UCG	
Increase cardiac chamber	19 (40.4)
Pericardial effusion	2 (4.25)
Decrease value of EF	38 (80.8)
X-ray of chest	
Cardiothoracic ratio	0.66±0.04

of length of hospital stay was 10-27 days, and the length of stay after the initiation of treatment ranged from 9 h to 7 days. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Jilin University. Written informed consent was obtained from all participants. Related data are shown in **Table 1**.

Inclusion and exclusion criteria

The selected children were those with a diagnosis of FM with rapid progression of disease and severe hemodynamic changes. The following inclusion criteria were used: (i) tachycardia with a heart rate >2 standard deviations above normal (without external stimulus, chronotropic drugs, or pain), or progressive bradycardia lasting >0.5 h; (ii) systolic hypotension 2 standard deviations below the normal value for age without the use of vasoactive drugs; and (iii) monitoring of central venous pressure (CVP). All children with a history of congenital cardiovascular malformations, as well as children with malignant tumors, metabolic diseases, and chromosomal disorders, were excluded.

Case selection

Children with FM who were admitted to the hospital without having undergone CBP were set as the control group (n = 16) and received standard care. The controls included 10 boys and 6 girls aged 3 months to 9 years with a weight range of 3.8-17 kg. The intervention group consisted of 31 children with FM who received standard care plus CBP. The intervention group included 17 boys and 14 girls aged 2

Table 2. Catheter selection of children with different weight

Weight	Diameter	Lumen
<6 kg	4~5 F	Single
6~12 kg	6.5~7.5 F	Double
12~20 kg	8.5~9 F	Double
>20 kg	9~11 F	Double

Table 3. Selection of filtering membrane area and filter of children with different weight

Weight	Membrane area	Filter
<3 kg (infants)	0.1 m^2	AV paed
<20 kg	0.2-0.3 m^2	AV 400 S
>20 kg	0.4-0.6 m^2	AV 600 S

months to 14 years with a weight range of 4.4-40 kg.

Data collection

Laboratory examinations including those for C-reactive protein, N-terminal pro-B-type natriuretic peptide, myocardial enzymes, and blood gas analysis were performed on admission. These examinations were repeated at 48 and 72 h after treatment. The vital signs (temperature, heart rate, blood pressure, respiration, CVP), electrocardiogram (ECG), echocardiogram (chamber dimensions, ejection fraction [EF] value, cardiac output, chest wall motion, and presence or absence of pericardial effusion), and chest radiograph (cardio-thoracic ratio) of all study subjects were recorded on admission and at 48 and 72 h after admission.

Intervention

Children in the control group were given standard support including ECG monitoring, ventilation, sedation, and usual treatment. The controls were treated with antiviral agents (ganciclovir and vidarabine), creatine phosphate sodium for myocardial nutrition, and digitalis and diuretics. Dopamine, norepinephrine, and other vasoactive drugs were added to increase cardiac output and support blood pressure. Patients were given high-dose corticosteroids (10 $mg \times kg^{-1} \times day^{-1}$, 3 days) and intravenous immunoglobulin (1 $g \times kg^{-1} \times day^{-1}$, 2 days) to modulate their immune responses once at admission. Children with a low heart rate were given isoproterenol, as a temporary pacemaker could be implanted due to the existence of a third compartment. Lidocaine was administered in patients with ventricular tachycardia.

In addition to the above treatment, the intervention group was also treated with CBP. Written informed consent was obtained from all families. Extracorporeal circulation was established by inserting a single-needle double-lumen catheter in the femoral vein, with the type of catheter chosen according to the weight of the patient as shown in **Table 2**. Fresenius (Fresenius Medical Care AG, Frankfurter, Germany) polysulfone membrane transfusion filters were selected with the choice of filtrate according to the patient's body surface area, as shown in **Table 3**. The Fresenius Multifiltrate was used in the continuous venovenous hemodiafiltration/continuous venovenous hemofiltration (CVVHDF/CVVH) mode. Heparin sodium (30 U/kg) was given before CBP treatment, and CBP was performed after the activated clotting time (ACT) exceeded 160 s. During treatment, 10-20 U/kg heparin sodium was continuously infused to maintain the ACT in the range of 160-180 s (activated partial thromboplastin time [APTT], 60-80 s). The initial flow velocity of blood was 10-20 mL/min and gradually increased to the target velocity of 3-5 $mL \times kg^{-1} \times min^{-1}$. The velocity of replacement fluid was 30-50 $mL \times kg^{-1} \times h^{-1}$, and the flow rate of the dialysis fluid was 25-50 $mL \times kg^{-1} \times h^{-1}$. The treatment parameters and content of the dialysate were adjusted on a per-patient basis.

Vasoactive agents were used as required, including adrenaline (0.1-0.3 $mg \times kg^{-1} \times min^{-1}$), dopamine (10-15 $mg \times kg^{-1} \times min^{-1}$), and milrinone (0.5 $mg \times kg^{-1} \times min^{-1}$). Colloidal fluids (suspension of red blood cells, human serum albumin, or hydroxyethyl starch 130/0.4 sodium chloride injection) were used to expand systemic capacity to avoid a rapid decrease of blood pressure at the initial stage of CBP treatment. In the some cases, digoxin was used to improve the function of the left ventricle. During treatment with CBP, patient responses were evaluated by monitoring vital signs and laboratory indicators, and the CBP treatment time was adjusted accordingly. When cardiac function and circulatory stability were restored, the dose of vasoactive drugs was gradually tapered and CBP treatment was stopped.

Table 4. The changes of vital signs in two groups of children survived

Index	Group	n	Before treatment	48 h after treatment	72 h after treatment
Heart rate (times/minute)	Control	9	194.89±17.87	161.11±14.92	138.44±5.77*
	Experiment	26	202.23±15.07	158.56±15.19*	132.64±4.54
Respiration (times/minute)	Control	9	57.23±27.05	40.63±15.72	31.58±6.27*
	Experiment	26	61.42±13.51	38.13±9.26*	29.65±7.32
CVP (cmH_2o)	Control	9	11.71±1.90	10.68±1.23	9.58±1.23*
	Experiment	26	12.33±2.01	10.12±0.92*	7.84±0.83**

Note: *Compare with the condition before treatment, P<0.05, **Compare with the condition before treatment, P<0.01.

Table 5. Comparison of laboratory examination indicators in two groups of children with survived

Index Indicator	Group	n	Before treatment	48 h after treatment	72 h after treatment
Troponin (ng/mL)	Control	9	3.23 (2.17, 5.9)	2.42 (1.78, 3.14)	1.01 (0.69, 1.35)*
	Experiment	26	5.06 (2.78, 6.44)	3.27 (1.86, 3.74)*	0.71 (0.63, 1.12)
Myoglobin (ug/L)	Control	9	521.90 (286.90, 610.1)	347.02 (207.10, 414.46)	212.23 (120.45, 250.34)**
	Experiment	26	793.46 (563.51, 1346.34)	510.56 (237.35, 702.12)**	201.27(124.09, 354.66)
CKMB (ng/mL)	Control	9	431.90 (336.98, 476.44)	248.28 (216.46, 302.35)*	110.22 (99.11, 141.43)
	Experiment	26	442.04 (343.70, 585.33)	247.11 (191.35, 267.40)**	98.37 (51.29, 113.20)
CK (IU/L)	Control	9	485.70 (371.31, 802.11)	309.67 (249.67, 410.16)	182.36 (146.28, 202.42)*
	Experiment	26	594.00 (553.36, 1706.04)	325.01 (296.31, 1221.00)*	148.48 (123.80, 567.44)
NT-proBNP (pg/ml)	Control	9	8747.0 (5194.0, 11060.0)	6201.0 (5001.0, 8933.0)	3891.0 (2691.0, 5440.0)*
	Experiment	26	30744.0 (9780.0, 10.0900.0)	14633.0 (5776.0, 63420.0)**	5267.0 (4603.0, 29002.0)
WBC ($\times 10^9$/L)	Control	9	17.94 (2.93, 25.56)	13.88 (3.80, 21.02)	8.90 (3.86, 16.54)**
	Experiment	26	17.62 (3.68, 23.33)	14.1 (3.67, 17.33)*	7.49 (3.99, 14.54)
LAC (mmol/L)	Control	9	5.10 (1.70, 5.90)	3.10 (1.30, 4.60)*	1.70 (1.30, 4.30)
	Experiment	26	7.30 (2.80, 13.50)	2.70 (1.88, 5.70)**	1.50 (1.30, 2.20)
AST (u/L)	Control	9	172.15 (78.68, 219.33)	127.66 (79.20, 144.58)*	64.84 (50.38, 95.94)*
	Experiment	26	1195.75 (770.78, 1255.05)	633.85 (373.28, 885.78)*	217.80 (195.42, 298.74)

Note: *Compare with the condition before treatment, P<0.05, **Compare with the condition before treatment, P<0.01.

Statistical analysis

Data were analyzed by using the statistical software package SPSS 20.0 (IBM, Armonk, NY, USA), and nonnormal data were measured as median (interquartile range), P_{50} (P_{25}, P_{75}). Normally distributed data were measured as $\bar{x}$ ±s. Paired t-test was used for measurement data. Wilcoxon rank sum test and independent-sample Mann-Whitney U-test were used for comparisons between the two groups. P<0.05 was considered statistically significant.

Results

Forty-seven children with FM, including 27 boys and 20 girls, were enrolled in the study. The age range was 2 months to 14 years with a median age of 14.35 (8.00, 32.50) months. The weight range was 3.8-4.0 kg with a median weight of 12.70 (6.70, 15.75) kg. The differences in age and weight between the groups were not statistically significant (P>0.05). In the control group, 9 children with FM survived and 7 died (mortality rate, 43.75%), whereas in the intervention group, 26 children with FM survived and 5 died (mortality rate, 16.13%). The average hospitalization time of the control group and the intervention group was 20.38±4.59 days and 16.05±2.13 days, respectively, and the difference was statistically significant (P<0.01).

Improvements were seen during 24-48 h in heart rate, respiration, CVP, and other vital signs in the survivors in both groups (**Table 4**). Two patients with cardiogenic shock died, whereas three patients survived in the intervention group. After CBP treatment for 24-48 h, the blood pressure of the survivors gradually increased to within the normal range. In both groups, there were varying degrees of improvement in children with ventricular arrhythmia,

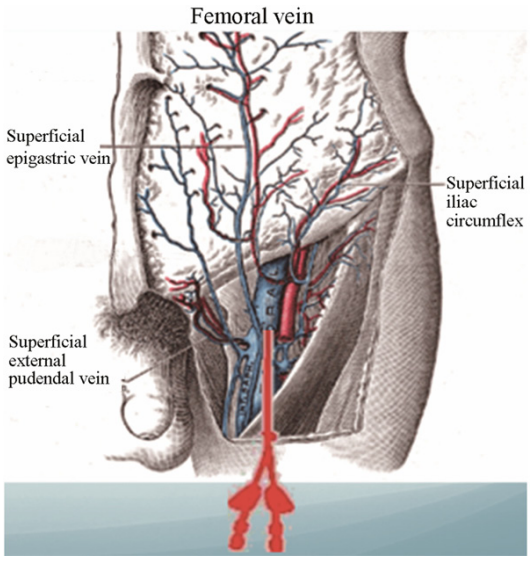

Figure 1. Diagram of femoral vein puncture.

atrioventricular block, and other abnormal changes of ECG after active treatment. The cardio-thoracic ratio of the children increased initially, and then gradually recovered after active treatment (0.57±0.03). The EF in both groups initially decreased significantly on echocardiography (25-32%), and then gradually increased to 31-38% after treatment. Cardiac chamber enlargement (particularly enlargement of the left ventricle and atrium) and pericardial effusion progressively reduced. There were no significant differences in the changes of ECG, chest radiograph, and echocardiogram findings (P>0.05).

The levels of laboratory indicators of myocardial injury were significantly elevated initially and decreased after treatment, as shown in **Table 5**. Significant improvements (P<0.05) were seen in the levels of myoglobin, MB isoenzyme of creatine kinase (CKMB), NT-proBNP, and lactic acid (P<0.01). After standard treatment for 72 h, the laboratory parameters of children with FM in the control group improved significantly, whereas those in the CBP group showed significantly more rapid improvement of laboratory parameters. During CBP treatment in the intervention group, there were four cases of hypotension (12.9%), six cases of hypothermia (19.35%), three cases of severe exudation at the injection site (9.67%), five cases of hematuria (16.13%), nine cases of decreased platelets (29.03%), and one case of deep vein thrombosis (3.23%). No fistulae at the puncture site or catheter-related infections occurred, and no allergic reactions or aeroembolism developed.

Discussion

With acute onset, FM can rapidly result in hemodynamic deterioration and severe myocardial injury with a high associated mortality rate [1, 7, 9]. The efficacy of conservative treatment with drugs is not ideal. CBP can effectively improve hemodynamics, remove systemic inflammatory mediators, rapidly correct acid-base imbalances, and improve the reactivity of blood vessels to vasoactive drugs [10-12], thus improving the chances for survival of children with FM.

CVVHDF/CVVH was selected as the treatment mode in this study as it is the standard mode of CBP for children [13]. Solute and water were removed continuously, osmotically, and slowly with CBP, and the changes in capacity and colloid osmotic pressure per unit of time were small. This approach ensures adequate perfusion of body tissues [14] and stable hemodynamics, an approach that is applicable to smaller critically ill children. In this study, we observed that the surviving children with FM benefitted from the stable hemodynamics of CBP treatment. In addition, removing inflammatory mediators nonspecifically by using a high-permeability membrane can block the inflammatory cascade in vivo, thereby relieving the systemic inflammatory reaction and improving the prognosis of children with FM [15]. The troponin, BNP, and CKMB of children in the intervention group increased rapidly to peak within 24 h, and then decreased rapidly after CBP especially in the first 48 h, suggesting that CBP treatment can effectively remove a number of inflammatory mediators in vivo and block the inflammatory cascade. The mortality of children with FM was considered to be associated with a delay in hospital admission, rapid progression of the condition, recalcitrant cardiogenic shock, and malnutrition or other underlying illnesses.

In this study, we encountered several challenges in the CBP treatment of children with FM, as follows: (i) determination of the earliest treatment time and the optimal duration of treatment; (ii) establishment of vascular access; (iii) anticoagulation in the process of treatment; (iv) ensuring stable hemodynamics during treat-

ment; (v) fluid and electrolyte balance; (vi) clearance of drugs; and (vii) complications.

For children with FM, there is no specific evidence-based recommendation for the timing of initiation of circulatory assistance in vitro. However, given the clinical experience demonstrated in this study, the decision of the time to start treatment is based on the accurate prediction of the development of clinical complications and the overall condition of the patient with FM. The decision cannot wait for the test indicators to achieve a certain degree of severity, or it will be too late to apply CBP treatment. Meanwhile, the length of time of CBP treatment can be adjusted according to factors such as the degree of functional recovery and the recovery of laboratory examination indicators. Clinicians are advised to monitor objective results and avoid repeated procedures that can lead to large fluctuations in blood volume and increased burden on the heart.

The establishment of good vascular access is a basic requirement for the process of CBP. It was relatively difficult for us to establish effective vascular access owing to the tenuous blood vessels of some of the patients, necessitating the selection of femoral venous punctures to place a catheter with a single needle and double lumen, as shown in **Figure 1**. For children with a low body weight and fragile veins, catheters with a single needle and a single lumen can be chosen to ensure the blood flow needed in the treatment [12, 16].

In this study, heparin sodium was used as an anticoagulant. The ACT/APTT was carefully monitored during treatment, and generally measured every 1-2 h to maintain an ACT result in the 160-180 s range (APTT, 60-80 s). Protamine was immediately administered in cases of bleeding [17, 18].

For hemodynamic control, vascular access and dialyzers for children were used to reduce the impact on the effective circulating blood volume in the early phases of treatment [14]. Objective evaluation of the patient condition, appropriate selection of the treatment line and mode, and sufficient preload can effectively promote the safety of treatment. For children with a low body weight, colloidal solutions can be used in the initial treatment in order to gradually improve perfusion. Physiological colloids such as a suspension of red blood cells are preferred. During treatment, the relative stability of the effective circulating blood volume should be maintained, and the rate of target therapy should be controlled at 30-50 mL/kg. The transmembrane pressures and pressures in the lines, arteries, and veins should be closely monitored to avoid stagnation of the blood in the extracorporeal circuit, which may result in thrombosis and hemorrhage. Vital signs and the volume of fluid per hour were closely monitored to avoid increasing the physiologic burden of the CBP treatment. In addition, blood gasses and calorie intake were monitored, and the internal environment and acid-base balance was adjusted regularly.

Pharmacological therapies such as anti-infectives and organ support are still needed in the process of CBP treatment. As drugs of small molecular weight or low protein binding rate can be cleared [19-21] through CBP, the dosages were adjusted during CBP treatment.

In this study, complications developed during CBP treatment, including hypotension, hypothermia, exudation at the injection site, hematuria, decreased platelets, and deep vein thrombosis. No fistulae at the puncture sites and no catheter-related infections occurred, and there were no incidences of allergy or aeroembolism. Before treatment, a full assessment of the effective circulatory volume was estimated and fluids were supplemented appropriately. Administration of vasoactive drugs may prevent the occurrence of hypotension. Hypothermia occurred in patients with a low body weight during treatment with CBP, which was considered to result from higher extracorporeal circulation volume and longer treatment times. We used double heaters before dialysis and filtration with the Fresenius blood purification machine. Adjusting the temperature appropriately and using external warming blankets can effectively protect patients from hypothermia.

To minimize bleeding with the use of heparin, careful monitoring of coagulation was required and the ACT range was strictly controlled during treatment. Moreover, fluctuations in blood platelet levels and in the pressure of arteries, veins, and transmembranes needed to be closely observed. Once the treatment finished, ultrasound of the deep veins as well as cathe-

ter cultures were obtained and addressed appropriately to avoid complications.

Owing to the small number of FM cases and the short amount of time patients spent at our department, there was no long-term follow-up performed. In addition, the levels of various cytokines in these patients should be studied in the future.

Conclusions

CBP can effectively stabilize the hemodynamics and reduce mortality in children with FM. The levels of myoglobin, troponin, BNP, and lactic acid in children with FM can be decreased significantly with CBP treatment.

Disclosure of conflict of interest

None.

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