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Plasma exchange parameter selection and safety observation of children with severe ricinism

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ABSTRACT. The aim of this study was to investigate the selection of plasma exchange (PE) parameters and the safety of children with severe ricinism. The PE parameters and heparin dosage in 7 children with severe ricinism were recorded, and changes in the patients' vital signs and coagulation function were monitored before and after PE. All patients successfully completed PE. The speed of blood flow was 50-80 mL/min, speed of exchange flow was 600-800 mL/h, and isolating rate of blood plasma was 12.5-19.05%. Transmembrane pressure was stable at approximately 100 mmHg, and venous pressure was stable at approximately 95 mmHg. The first dose of heparin was 0.39 ± 0.04 mg/kg, and the maintaining heparin dose was 0.40 ± 0.05 to 0.22 ± 0.03 $mg \cdot kg^{-1} \cdot h^{-1}$. During the PE process, mean arterial pressure, heart rate, respiratory rate, and pulse oxygen saturation were steady. After PE, the activated partial thromboplastin time and thrombin time prolonged to

2-3 times greater than that before PE. However, no bleeding tendency was seen. For children with severe ricinism, the choice of PE to eliminate the toxin from blood, tissues, and organs was safe and effective.

Key words: *Ricinus communis*; Ricinism; Plasma exchange (PE); PE parameters; Rescue treatment

INTRODUCTION

Ricinus communis refers to the seed of *R. communis* L., which contains two toxic ingredients, ricin and ricinine. Ricin is a cell protoplasmic poison with high toxicity, capable of damaging the parenchyma of the liver and kidneys in a short time, thus resulting in swelling, bleeding, and necrosis; it also aggregates and dissolves red blood cells, paralyzing the respiratory center and vasomotor center, and if rescue therapy is delayed, can lead to very serious consequences (Audi et al., 2005; Lim et al., 2009; Assiri, 2012). To date, no specific antidote or vaccine for ricin poisoning exists (Hu et al., 2012). Consequently, treatment primarily consists of induction of vomiting, gastric lavage, and catharsis, with some cases requiring a high enema (Musshoff and Madea, 2009; Buonocore et al., 2011) to quickly clear residual toxins from the digestive tract. However, general medical treatments cannot effectively clear toxins that have already entered the blood, tissues, or organs, especially in cases of multiple organ dysfunction. Plasma exchange (PE) is a blood purification method that removes blood from the body, then separates and removes the plasma *in vitro* and reinfuses an equal amount of exchange fluid back into the body. PE has played a major role in rescue treatment of critically ill patients and patients with autoimmune diseases (Inoue et al., 2010; Qiu et al., 2011; Qu et al., 2011). It is especially valuable in diseases associated with liver failure because of its demonstrated irreplaceable role in clearing toxins from the liver (Nakae et al., 2012). Theoretically, PE could clear almost all toxins from the plasma, especially those that couple tightly with plasma proteins (Schutt et al., 2012). When children, who have immature immune systems, are poisoned by ricin, the toxins should be removed as early and quickly as possible to reduce subsequent damage, mortality, and sequelae. However, because of difficult vascular access, higher technical requirements for anticoagulation, and the fear of hemodynamic changes, serum response, and transfusion-transmitted diseases, PE has rarely been used for rescue treatment of acute poisoning in children. In our hospital, 7 children with severe ricinism were treated with PE in November 2012, and all were cured without any organ system dysfunction or sequelae. In this paper, we report on parameter selection and safety during PE.

SUBJECTS AND METHODS

Clinical data

The 7 patients in this study were all school-age children, including 6 boys and 1 girl. Ages ranged from 7 years and 7 months to 8 years and 11 months, with a mean age of 8.17 ± 0.42 years. The lowest weight was 22.00 kg, and the highest was 31.20 kg, with a mean weight of 25.69 ± 3.17 kg. Except for one child who had an upper respiratory tract infection before eating the *R. communis*, the children were all healthy. The amount of raw *R. communis* mistakenly eaten was 5 to 12 pills. This study was conducted in accordance with the Declaration of

Helsinki and with approval from the Ethics Committee of Fuzhou General Hospital of Nanjing Military Command, PLA. Written informed consent was obtained from all participants.

Clinical manifestations

All the children in the study exhibited symptoms within 3 to 4 h after ingestion of *R. communis*. Gastrointestinal symptoms occurred first, appearing as nausea, vomiting and abdominal pain. The degree of vomiting varied from several times to more than 10 times. Four children developed diarrhea, and 1 child exhibited hemorrhagic colitis as the primary symptom. In addition to the gastrointestinal symptoms, a common manifestation was the appearance of cardiac symptoms: slowing of the heart rate, sinus arrhythmia, occasional atrial premature beats, and in 1 patient, significant bradycardia. Two children developed fever, with a body temperature of 38° to 39.5°C and fever duration of 24 to 36 h. One child exhibited apathy, lethargy, and hand tremor.

General treatment

All patients received conventional treatment, including induction of vomiting, gastric lavage, catharsis, fluid infusion, and fasting from fats and oils, and underwent PE within 30 to 91 h of ingestion of *R. communis*.

PE method

PE was performed using a BM25 continuous blood purification machine (Baxter Corp., USA), with supporting extracorporeal circulation pipelines and P1 dry plasma separator (membrane area 0.3 m^2, Fresenius SE & Co. KgaA, Bad Homburg, Germany). Using a femoral vein catheter (Arrow Electronics, Inc., USA), 25 U/mL heparinized saline was infused to circulate the vascular access for 30 min, then 100 mL pre-prepared red blood cell suspension (plasma-reduced blood), of the same blood type as the child, was injected into the vascular access and held there. The posterior substitution method was used. The exchange fluid was fresh frozen plasma of the same blood type as the child, and the exchange volume was 1440 to 1950 mL, with a mean of 1781.43 ± 168.27 mL.

Observation indicators

The speed of blood flow (SBF), speed of exchange flow (SEF), isolating rate of blood plasma (IF), transmembrane pressure (TMP), venous pressure (VP), and heparin dose (HPD) were recorded every 15 min. The plasma separation rate (%) = [(SEF / (SBF x 60)] x 100. The mean arterial pressure (MAP), heart rate (HR), respiratory rate (RR), and pulse oxygen saturation (SpO_2) were monitored and recorded every 15 min. The coagulation functions of the venous blood were monitored before and after PE.

Statistical analysis

The SPSS 11.0 statistical software was used for the statistical analysis. The measurement data are reported as means ± SD, the comparison of means at different times used the

single-factor repeated-measuring analysis of variance, and the coagulation changes used the paired *t*-test, with the test level (α) set as 0.05.

RESULTS

General information

All patients successfully completed PE. One child developed a rash 2 h after PE, and 2 children developed a rash during PE. The rashes all gradually disappeared 1 h after administration of promethazine hydrochloride and dexamethasone. After a 10-day hospitalization, all patients recovered and were discharged from the hospital. A 10-month follow-up revealed that none of the patients had systemic organ dysfunction or sequelae.

Changes of PE parameters

SBF was 50 to 80 mL/min, SEF was 600 to 800 mL/h, and IF was 12.5 to 19.05%. The TMP and VP were slightly higher after 30 min of PE than at other times, without significant difference ($P > 0.05$). The first HPD was 0.39 ± 0.04 mg/kg, and the maintenance HPD decreased gradually such that at 15 min before the end of PE, the HPD was significantly lower than that during the 15 to 75 min after PE was started ($P < 0.01$; Table 1).

Table 1. Comparison of the plasma exchange parameters (means ± SD, N = 7).

Time	SBF (mL/min)	SEF (mL/h)	IF (%)	TMP (mmHg)	VP (mmHg)	HPD $mg \cdot kg^{-1} \cdot h^{-1}$
15 min	64.29 ± 7.87	600.00 ± 0.00	15.78 ± 2.17	88.57 ± 24.10	77.14 ± 30.94	0.40 ± 0.05
30 min	69.29 ± 1.89	600.00 ± 0.00	14.44 ± 0.42	117.14 ± 40.71	104.29 ± 30.47	0.40 ± 0.14
45 min	70.00 ± 0.00	600.00 ± 0.00	14.29 ± 0.00	104.29 ± 11.34	94.29 ± 12.72	0.38 ± 0.14
60 min	70.00 ± 0.00	628.57 ± 75.59	14.97 ± 1.80	101.43 ± 13.45	92.71 ± 9.39	0.37 ± 0.11
75 min	71.43 ± 3.78	671.43 ± 95.12	15.73 ± 2.57	104.29 ± 7.87	95.71 ± 11.34	0.35 ± 0.11
90 min	71.43 ± 3.78	700.00 ± 100.00	16.41 ± 2.75	104.29 ± 11.34	98.57 ± 10.69	0.29 ± 0.07
105 min	71.43 ± 3.78	700.00 ± 100.00	16.41 ± 2.75	102.86 ± 17.04	95.71 ± 12.72	0.28 ± 0.07
120 min	71.43 ± 3.78	700.00 ± 100.00	16.41 ± 2.75	105.71 ± 15.12	92.86 ± 13.80	0.28 ± 0.07
135 min	71.43 ± 3.78	700.00 ± 100.00	16.41 ± 2.75	105.71 ± 16.18	94.29 ± 12.72	0.25 ± 0.04
150 min	71.43 ± 3.78	700.00 ± 100.00	16.41 ± 2.75	105.71 ± 15.12	92.86 ± 13.80	0.23 ± 0.04
165 min	71.43 ± 3.78	700.00 ± 100.00	16.41 ± 2.75	100.00 ± 18.28	90.00 ± 18.26	0.22 ± 0.03
180 min	71.43 ± 3.78	700.00 ± 100.00	16.41 ± 2.75	100.00 ± 10.00	88.57 ± 10.69	0.00 ± 0.00
P	0.116	0.031	0.171	0.400	0.359	0.000

SBF = speed of blood flow; SEF = speed of exchange flow; IF = isolating rate of blood plasma; TMP = transmembrane pressure; VP = venous pressure; HPD = heparin dose.

Changes of the vital signs during PE

During PE, the patients' vital signs were stable: MAP, SpO_2, HR, and RR exhibited no statistically significant difference at each time point ($P > 0.05$; Figures 1-4).

Changes of coagulation function before and after PE

The post-PE prothrombin time (PT) and international normalized ratio of PT (PT-INR) exhibited a trend of prolongation but without significant difference ($P > 0.05$); the post-PE acti-

vated partial thromboplastin time (APTT) and thrombin time (TT) were significantly longer ($P < 0.05$); and the post-PE fibrinogen was significantly reduced ($P < 0.01$; Table 2).

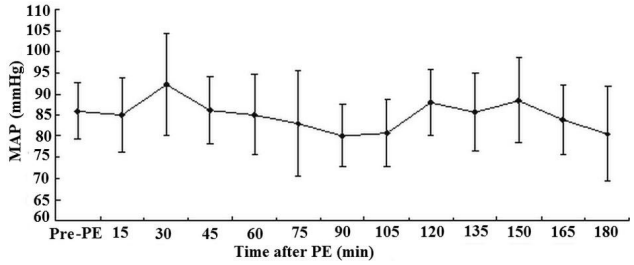

Figure 1. Changes of mean arterial pressure (MAP) in plasma exchange (PE) treatment.

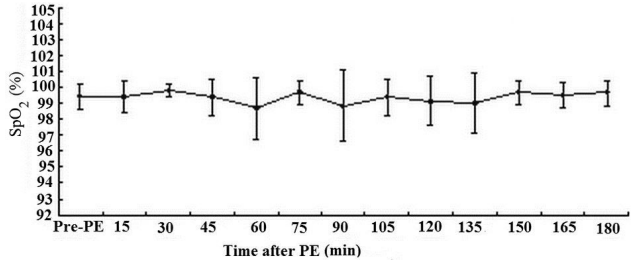

Figure 2. Changes of pulse oxygen saturation (SpO_2) in plasma exchange (PE) treatment.

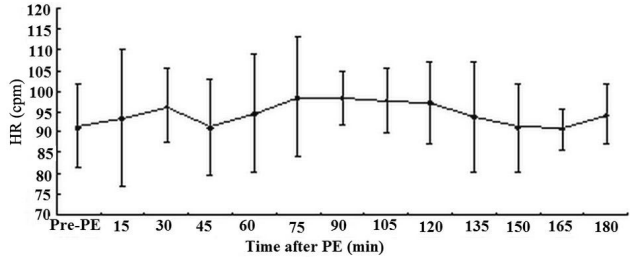

Figure 3. Changes of heart rate (HR) in plasma exchange (PE) treatment.

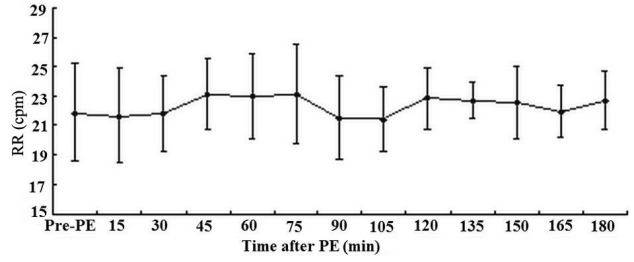

Figure 4. Changes of respiratory rate (RR) in plasma exchange (PE) treatment.

Table 2. Changes of coagulation function before and after plasma exchange (PE) treatment (means ± SD, N = 7).

Time	PT (s)	PT-INR	APTT (s)	TT (s)	FB (g/L)
Pre-PE	12.14 ± 0.93	1.04 ± 0.08	26.13 ± 4.00	16.17 ± 0.93	2.86 ± 0.40
Post-PE	13.90 ± 2.28	1.18 ± 0.18	68.26 ± 32.30	47.13 ± 34.54	1.83 ± 0.34
T	-1.884	-1.885	-3.425	-2.370	5.182
P	0.084	0.084	0.013	0.055	0.000

PT = prothrombin time; PT-INR = international normalized ratio of PT; APPT = activated partial thromboplastin time; TT = thrombin time; FB = fibrinogen.

DISCUSSION

PE was initially used for the treatment of liver diseases, providing valuable time for autogenic liver cell repair and for patients awaiting liver transplantation, especially for patients with acute liver failure (Stenbøg et al., 2013). In recent years, with increased understanding of disease pathogenesis and PE technology, PE indications have gradually expanded into neurology, hematology, critical care medicine, rheumatology, dermatology, and other fields (Erkurt et al., 2013; Kaya et al., 2013), but experience in pediatric applications is limited. The most toxic ingredients in *R. communis* are ricin and ricinine (Brandon et al., 2012). Ricinine is water-soluble, with a relative molecular mass of 164.16 daltons; therefore, it can be eliminated through hemodialysis, hemofiltration, or peritoneal dialysis. However, ricin is a large protein molecule formed by the connection of an A-chain (RTA) and B-chain (RTB) through a disulfide bond (Balint, 1974; Challoner and McCarron, 1990; Roche et al., 2008), and its relative molecular weight is 65 kilodaltons. Such a large molecule cannot be eliminated through the above blood purification measures (convection and diffusion theory) and can only be cleared through PE. Although blood perfusion could broadly clear such toxins as ricin and ricinine, the adsorbent materials in this treatment would directly contact the patient's blood cells and could lead to dynamic instability of the blood during the procedure. Therefore, the risk of this approach is relatively large.

The most common complications reported with PE are nausea, vomiting, hypotension, abdominal pain, and pruritus (Erkurt et al., 2013), and rare complications are serum response and venous thrombosis (McGuckin et al., 2014). During PE, the MAP, HR, RR, and SpO_2 of the children in our study were stable, with almost no significant changes in vital sign parameters at each time point. One of the 7 children exhibited a rash 2 h after PE, and 2 children exhibited rashes during PE. The rashes all gradually disappeared 1 h after the administration of promethazine hydrochloride and dexamethasone. The rest of the children had no discomfort, and all successfully completed the PE, indicating that with skilled and careful technical preparation, PE can be very safe in the rescue treatment of poisoning in children. The children in the study group underwent PE before significant organ dysfunction appeared, and the general condition of all the children was good, which contributed to PE safety. If the PE had been performed in the presence of significant organ dysfunction or circulatory failure, the risk would have increased, and the final prognosis would have been affected.

Anticoagulation is the key to successful blood purification (Naumnik et al., 2009; Shen and Winkelmayer, 2012). If anticoagulation is not adequate to obtain sufficient heparinization of the systemic blood, the TMP and VP might abnormally elevate, causing clotting of the filters and piping. An excessively high TMP could also cause hemolysis of the red blood cells. However, the opposite situation of excessive anticoagulation due to an excessive HPD would lead to bleeding. In our research, the initial HPD for the 7 children was 0.39 ± 0.04 mg/

kg, and maintenance doses were 0.40 ± 0.05 to 0.22 ± 0.03 $mg \cdot kg^{-1} \cdot h^{-1}$, with a total dose of 1.33 ± 0.39 mg/kg. The HPD was generally larger than that given to adults. No hemolysis occurred during the PE. The post-PE APTT, and TT prolonged to 2-3 times their values pre-PE, but no bleeding phenomena were seen in the skin puncture site or internal organs, and 8 h later, all the indicators returned to normal. This suggests that the children were in a growth and development period, with unstable coagulation function; therefore, the HPD required individualization. During the PE process, the TMP, VP, and color of the filters should be closely observed, and coagulation function should be closely monitored to prevent excessive anticoagulation-induced bleeding and insufficient coagulation-induced red blood cell destruction and hemolysis.

Regarding TMP and SBF, the TMP should be maintained at <100 mmHg for adults to prevent hemolysis, and the SBF must be >50 mL/min to avoid coagulation inside the hollow fibers of the membrane. The ideal SBF might be 100 to 150 mL/min. Because central veins are smaller in children, a central venous catheter with a small diameter must be used. In this research, an 8-Fr central venous catheter was selected, with the SBF maintained at 60 to 70 mL/min. The TMP and VP at 30 min were 117.14 ± 40.71 and 104.29 ± 30.47 mmHg, respectively, and were slightly higher than those at the other time points. At other time points, the TMP was stable at approximately 100 mmHg, the VP was stable at approximately 95 mmHg, and the TMP was slightly higher than that of an adult. The higher TMP might have occurred because the membrane area of the child-type plasma separator is smaller than that used for adults, causing the blood to flow faster inside the hollow fibers. However, during the PE, no hemolysis or coagulation occurred, suggesting that when applying PE to children and closely monitoring coagulation functions, it is unnecessary to pursue a very low TMP, or use excessive anticoagulant, which must be avoided to prevent bleeding.

To improve exchange efficiency and save the plasma, the posterior exchange method of PE is often used. This requires more anticoagulation than the prior exchange mode; thus, the dose of anticoagulant used is relatively large. In this circumstance, we considered that it would be more important to control the SEF and IF. If the SEF was too fast, and the IF was too large, the blood would gradually thicken when flowing from the arterial end to the venous end inside the plasma separator, and the blood flow rate would gradually slow down, which could easily result in coagulation and erythrocyte rupture (Basic-Jukic et al., 2005). In this research, the patients' SEF was maintained at 600 to 700 mL/h, and the IF was controlled at approximately 15% during the PE process. No abnormal elevation of TMP and VP occurred, and no patient exhibited coagulation or hemolysis, suggesting the importance of controlling the SEF and IF and also suggesting that the amount of anticoagulant was appropriate.

In summary, for children with acute poisoning, especially from biological toxins with complex composition, larger molecular weight, and high affinity for plasma proteins (e.g., fish guts, *R. communis*, snake bites, and poisonous mushrooms), PE is safe and effective for purging toxins from the blood, tissues, and organs, and should be widely applied. When considering PE, it is unnecessary to wait for clinical organ failure to occur; PE should be performed as soon as possible so as to remove toxins and reduce subsequent damage, thus reducing mortality and sequelae, and improving the success rate.

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