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Case report

Artificial liver support system in pediatric acute liver failure due to mushroom poisoning: Case series

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ABSTRACT

Pediatric acute liver failure (PALF) due to mushroom poisoning is a rare and life-threatening disease. There is no specific treatment. Plasma exchange (PE) is often used as a bridge to the regeneration of the liver or transplantation. However, PE is limited due to an inadequate plasma supply and transfusion-related risks. The double plasma molecular adsorption system (DPMAS) can adsorb toxins, including bilirubin and inflammatory mediators. However, the DPMAS cannot improve coagulation disorders. Combining PE and the DPMAS could compensate for the shortcomings of the two techniques. A previous study showed that the combination might be more effective than using PE or the DPMAS alone in patients with mild acute-on-chronic liver failure. To the best of our knowledge, few studies combined PE and the DPMAS for the treatment of PALF due to mushroom poisoning. Here, we specifically describe our experience with PE and the DPMAS in PALF. In conclusion, our study shows that the DPMAS and PE are safe and effective in reducing the bilirubin level and improving blood coagulation in PALF due to mushroom poisoning as a bridge to transplantation or recovery.

Introduction

Pediatric acute liver failure (PALF) is characterized by biochemical evidence of acute liver injury and hepatic-based coagulopathy without a preceding chronic liver disease and is diagnosed within 8 weeks of disease onset in children [1,2]. PALF is a rare disease. Incidence of PALF in USA is around 5.5/million/year [3], but no epidemiological data in China. The roughly estimated incidence rate is 7–10 /million/year in our province. PALF is a life-threatening disease with mortality rates ranging from 24% to 75% [4]. Mushroom poisoning is a rare cause [5]. Over 90% of fatal mushroom poisonings worldwide are caused by Amanita species [6]. The main mechanism attributed to amatoxins is the ability to inhibit RNA polymerase II activity in the nucleus, and the decline in mRNA levels leads to a decrease in protein synthesis and, ultimately, cell death [7]. Failing hepatocytes are unable to clear metabolites from the blood, leading to the accumulation of toxic metabolites and a decrease in the hepatic capacity to synthesize coagulation factors, complement, and lipoproteins, which may cause multiple organ dysfunction syndrome (MODS) and finally death. There is no specific treatment for PALF due to mushroom poisoning. Liver transplantation is the only lifesaving treatment, but it is limited by the lack of donors [5]. The liver has a strong potential for liver regeneration. Therefore, it is rational to utilize a system that can replace liver functions until either spontaneous recovery occurs or a suitable donor liver becomes available for liver transplantation in those with definite indications. An artificial liver support system is often used as a bridge to the regeneration of the liver or liver transplantation, and plasma exchange (PE) is the most widely applied modality [8]. However, PE is often limited due to an inadequate plasma supply [9] and carries transfusion-related risks. Therefore, clinicians are actively searching for more effective and less risky modalities.

The double plasma molecular adsorption system (DPMAS) can adsorb medium-sized and macromolecular toxins, including bilirubin, to improve jaundice and slow the deterioration of acute liver failure. Because no extra plasma is used, transfusion-related risks can be avoided, and plasma can be saved. However, the DPMAS cannot improve coagulation disorders [10]. Combining PE and the DPMAS could compensate for the drawbacks of the two techniques and may be a promising treatment for PALF.

A previous study showed that the DPMAS and PE might be more effective than PE or the DPMAS alone in acute-on-chronic liver fail-

Abbreviations: PALF, pediatric acute liver failure; MODS, multiple organ dysfunction syndrome; PE, plasma exchange; DPMAS, double plasma molecular adsorption system; HE, hepatic encephalopathy; INR, international normalized ratio; LIU, Liver Injury Units.

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ure patients. Another study also suggested that PE and the DPMAS were safe and required a lower quantity of plasma [9,10].

However, children are not miniature versions of adults. Hepatic encephalopathy (HE) appears late in patients with PALF, and some infants or younger children with PALF do not even have HE. This is the main difference between pediatric and adult acute liver failure. The main technical challenge on pediatric DPMAS or PE is the difficulty in establishing vascular access. In addition, there is no special equipment for children, so children are more likely to develop hemodynamic instability with adult equipment. Moreover, due to the inaccurate expression of younger children, the detection and treatment of complications are difficult. To the best of our knowledge, few studies reported the use of the DPMAS and PE in PALF [4]. Here, we described our experience using the DPMAS and PE in the treatment of PALF due to mushroom poisoning as a bridge to transplantation or recovery.

Materials and methods

Patients

This study is a retrospective observational study. Between 2012 and 2019, 11 pediatric patients were diagnosed with PALF caused by mushroom poisoning in the pediatric intensive care unit of the First Hospital of Jilin University. Among these patients, 3 patients with incomplete clinical data and 1 patient who died within 24 h after admission were excluded. 2 patients who only underwent PE were also excluded. 5 patients who received DPMAS and PE were included in this study. This report was approved by the ethics committee of the First Hospital of Jilin University, and informed consent regarding the use of anonymous data was obtained from all patients' guardians upon admission.

PALF was defined based on the following PALF study group criteria: (1) children with no known evidence of chronic liver disease; (2) biochemical evidence of acute liver injury; and (3) hepatic-based coagulopathy [prothrombin time $\geq$15 s or international normalized ratio (INR) $\geq$1.5 not corrected by vitamin K in the presence of clinical hepatic encephalopathy or prothrombin time <20 s or INR $\geq$ 2.0 regardless of the presence or absence of clinical HE] [4].

To investigate the etiology of PALF, precise history including toxin and/or drug exposure was taken, and serological viral screening (HAV, HBV, HCV, CMV, EB) was performed. Possible metabolic disorders, autoimmune liver diseases, ultrasound imaging and/or CT imaging were also evaluated. All patients had no history of drug or herbal intake and were not suspected of drug-induced liver injury, so RUCAM 2016 was not used. The diagnosis of mushroom poisoning was based on gastrointestinal symptoms after the ingestion of wild mushrooms and the absence of other possible causes.

Treatment

Comprehensive medical treatment

All patients received comprehensive medical treatment, including penicillin G and silybin use, energy and vitamin supplementation, and blood product supplementation, such as albumin, plasma and prothrombin complex. Appropriate supportive treatment, such as mechanical ventilation and vasopressors, was given as needed.

DPMAS and PE

Blood access was established by placing a double-lumen catheter into the left or right femoral vein. The size of the catheter varied depending on the patient's age.

PE was performed using a continuous renal replacement machine (MultiFiltrate, Fresenius Medical Care AG&Co. KGaA, Germany), an extracorporeal circuit (MPS Substituate System multiFiltrate, Fresenius Medical Care AG&Co. KGaA, Germany), and a membrane filter (Plasma Flux P2 dry, Fresenius Medical Care AG&Co. KGaA, Germany). No anticoagulants were used. PE using 50 mL/kg fresh frozen plasma per treatment course was implemented for 2 h. After admission, if the patient met the diagnostic criteria for PALF and the parents' consent was obtained, preparation for PE was initiated. However, the actual starting time of PE depended on whether sufficient suitable plasma was available. The PE interval was 1–2 days depending on the improvement in coagulation and whether enough suitable plasma for exchange was available.

The DPMAS was applied using a continuous renal replacement machine (MultiFiltrate, Fresenius Medical Care AG&Co. KGaA, Germany), a hemoperfusion machine (JF—800A, Zhuhai Health Sails Biotechnology Co., Ltd., Zhuhai, China), an extracorporeal circuit (MPS Substituate System multiFiltrate, Fresenius Medical Care AG&Co. KGaA, Germany), and a membrane filter (Plasma Flux P2 dry, Fresenius Medical Care AG&Co. KGaA, Germany). The DPMAS combines two types of absorbents, i.e., absorption resin (HA330-II, Zhuhai Health Sails Biotechnology Co., Ltd., Zhuhai, China) and ion exchange resin (BS330, Zhuhai Health Sails Biotechnology Co., Ltd., Zhuhai, China), for the plasma adsorption therapy. No anticoagulants were used. Each session of the DPMAS was 2 h. The main indication for the DPMAS in our institution was severe hepatitis with an obvious increase in bilirubin without coagulation disorder. However, when patients with PALF were unable to undergo PE due to the lack of plasma, the DPMAS was used first.

PE and the DPMAS were used until liver function improved and coagulation function was normal. Due to the limitations of laboratory conditions, we did not measure any proinflammatory surrogate markers. Since the duration of each PE or DPMAS was only 2 h, and the interval was not fixed, we did not specially make pharmacological adjustments.

Measurements

The patient records in the institutional electronic health record were manually abstracted. The patient data included demographic features, clinical manifestations, laboratory evaluations, and PE and DPMAS durations. The laboratory evaluation included alanine aminotransferase, total bilirubin, direct bilirubin, prothrombin time, INR, and ammonia. The laboratory evaluations measured the peak values before the DPMAS and PE and the values immediately after the final DPMAS or PE. The HE grade was defined using the West Haven Criteria [11]. The Liver Injury Units (LIU) Scoring System was used to evaluate the severity of PALF before and after the DPMAS and PE. LIU was calculated as LIU = (3.507 $\times$ peak total bilirubin) + (45.51 $\times$ peak INR) + (0.254 $\times$ peak ammonia) [12]. LIU was manually calculated through investigator chart review on patients. Because of the small sample size, we only make statistical description.

Results

Five patients were included in this study. The patients' age varied from 5 to 10 years. Four patients were female. All patients presented with vomiting and diarrhea as the initial symptoms. In addition to PALF, two patients had other complications, one was MODS, the other was acute pancreatitis. Regarding HE, 2 cases were categorized as grade IV. Among these patients, one died, and the other underwent LT. The length of hospitalization ranged from 3 to 21 days. The patient characteristics and outcomes are shown in Table 1. Regarding the DPMAS and PE, PE was applied once in one patient and twice in the other patients. The DPMAS was applied from one to 3 times, with a median of one application. The labo-

Table 1
Patient characteristics and outcomes.

	Age	Gender	Initial symptoms	Complications	HE Grade	PE (times)	DPMAS (times)	Days in ICU	Outcome	Follow-up period
Patient 1	10 y	Female	vomiting, diarrhea	MODS	IV	1	1	3	dead	NA
Patient 2	5y	Female	vomiting, diarrhea		III	2	2	12	alive	6 years
Patient 3	6y	Female	vomiting, diarrhea		II	2	2	17	alive	4 years
Patient 4	7y	Female	vomiting, diarrhea	pancreatitis	III	2	3	14	alive	2 years
Patient 5	9y	Male	vomiting, diarrhea		IV	2	2	21	LT	1 years

Abbreviation: NA: not available; MODS: multiple organ dysfunction syndrome; HE: Hepatic encephalopathy; DPMAS: the double plasma molecular adsorption system; PE: plasma exchange; LT: liver transplantation. ICU: intensive care unit.

Table 2
The laboratory results and LIU between the peak values before DPMAS + PE and just after the last DPMAS + PE.

	LIU		ALT (U/L)		TBIL (μmol/L)		INR		Ammonia (μmol/L)	
	Before	After	Before	After	Before	After	Before	After	Before	After
Patient 1	>437*	352	9504	1404	443	190	No clotting	5.5	75	50
Patient 2	309	88	4222	333	390	94	3.7	0.9	107	78
Patient 3	297	77	4062	963	291	37	3.9	1.0	98	59
Patient 4	393	118	6711	893	252	64	6.0	1.7	53	49
Patient 5	>426*	306	440	377	390	195	No clotting	4.5	115	83

Abbreviation: ALT: alanine aminotransferase; TBIL: total bilirubin; PT: prothrombin time; INR: international normalized ratio; DPMAS: the double plasma molecular adsorption system; PE: plasma exchange, LIU: Liver Injury Units.
Normal range: ALT: 0–40 U/L; TBIL: 0–21 μmol/L; INR: 0.8–1.2 μmol/L; Ammonia: 9–47 μmol/L.
* Calculate LIU with the upper limit of INR.

ratory results related to liver dysfunction and LIU were improved after the DPMAS + PE treatment (Table 2). There were no serious complications, such as hypotension and anaphylaxis, during the DPMAS. During the PE, patient 4 had one episode of an allergic rash, which disappeared after intravenous dexamethasone.

Discussion

PALF caused by mushroom poisoning is a rare and lethal condition with a very poor prognosis. There is no specific treatment. An artificial liver support system is often used as a bridge to the regeneration of the liver or transplantation. In a previous study, combining PE and the DPMAS was a promising treatment for acute liver failure [9,10,13]. To the best of our knowledge, few studies described the successful use of the DPMAS and PE in PALF. Here, we present a case series using the DPMAS and PE for PALF secondary to toxic mushroom ingestion to increase attention and facilitate further studies.

Amatoxin is the most important toxin in Amanita species. There are three distinct phases of amatoxin toxic syndrome as follows: 1) gastrointestinal phase: 6–24 h after ingestion; gastrointestinal symptoms include nausea, vomiting, abdominal pain, and diarrhea, and this phase lasts approximately 12−36 hours; 2) false "recovery" period: the gastrointestinal symptoms disappear; however, liver function gradually begins to deteriorate; and 3) hepatorenal phase: this phase occurs after 48 h and is characterized by hepatic dysfunction and even acute liver failure. Patients may develop jaundice, profound coagulopathy and rapidly progressing HE. Amatoxin toxic syndrome can be associated with MODS during this phase. Death may occur within 3–7 days after mushroom ingestion, while surviving patients recover within 14–21 days [14]. In this study, all patients had gastrointestinal symptoms as the initial symptoms. Patient 1 was complicated with MODS, and patient 4 was complicated with acute pancreatitis. Previous studies have suggested that the alanine aminotransferase, peak INR, and bilirubin levels and high-grade HE are predictors of mortality in patients with amatoxin intoxication [1]. Here, we confirm this observation. In this study, patient 1 had grade IV HE and MODS, and his alanine aminotransferase, total bilirubin, and INR levels were significantly higher than those of the other patients. Patient 1 died 3 days after admission.

Traditional supportive treatment for mushroom poisoning includes a gastric lavage, activated charcoal, biliary drainage, N-acetylcysteine, silymarin, etc. [15]. However, there is no evidence from randomized trials supporting the effectiveness of the therapy for PALF due to mushroom intoxication. The standard medical treatment for PALF includes energy and vitamin supplementation, optimal supportive care, infection control and avoidance of bleeding [16]. Liver transplantation is the only lifesaving treatment. However, liver transplantation is limited by donor liver shortage, high cost, and complications after transplantation. Therefore, liver transplantation is unlikely to be the first choice for PALF treatment.

The liver has a strong potential for liver regeneration. An artificial liver support system is often used as a bridge to the regeneration of the liver or transplantation. PE is the most widely applied modality and usually indicated first due to its safety, effectiveness and easy operation [8]. PE removes some of the patient's plasma, which is replaced with equivalent amounts of fresh frozen plasma to remove a circulating pathogenic molecule and toxic substances [13,17]. PE has been shown to effectively reduce the bilirubin content and improve coagulation parameters in patients with fulminant liver failure [13,18]. However, PE is often limited due to an inadequate plasma supply [9] and can carry transfusion-related risks. The DPMAS is a relatively new technology that uses a plasma filter to continuously separate the plasma; the filtered plasma passes through the specific bilirubin adsorber BS330 and the macroporous resin hemoperfusion device HA330-II to specifically remove toxic metabolites, including bilirubin and inflammatory mediators. The plasma is finally transfused back to the body without donated plasma. However, the DPMAS cannot improve coagulation disorders [10]. Combining PE and the DPMAS could compensate for the drawbacks of the two techniques and may be a promising treatment for PALF. Previous studies have suggested that combining PE and the DPMAS can increase the clearance of bilirubin, prolong the interval of PE, save plasma, and reduce side effects in adults [9,10,19]. In PALF, data on extracorporeal systems is scarce and the timing between sessions is still unclear [16]. In this study, all patients, except for one patient who died on the third day after admission, received at least two treatment sessions with PE and the DPMAS. After PE and the DPMAS, the liver function and coagulation parameters of patients 2, 3, and 4 were significantly improved, and these patients ultimately survived. At admission,

patient 5 had a decreased transaminase content, increased bilirubin content, and grade IV HE, which was a manifestation of severe decompensation of liver function, and he needed emergency liver transplantation. However, this patient did not receive a liver donation at the time. He extended the waiting time through the DPMAS and PE and underwent a successful liver transplantation on the seventh day after admission.

Based on data from a large, multicenter cohort of patients with PALF, the LIU score was a better predictor of transplant-free survival. When peak LIU score using INR $\geq$ 370, survival without LT was 19.8% [12]. Here we confirm this observation. The admission LIU scores of patient 1 and 5 exceeded 370. One died and the other underwent liver transplant.

PE complications include transfusion-related complications, hypotension, lung injury [13], metabolic alkalosis, and encephaledema [10]. Only one minor adverse event was observed. This event was an episode of allergic rash during PE. DPMAS complications include hypotension and anaphylaxis. There were no obvious complications during the DPMAS sessions.

A limitation of this study was that it was a retrospective observation of an uncontrolled experience with a small number of patients in one institution. Our experience shows that the DPMAS and PE are effective for PALF due to mushroom poisoning, but whether the combination can reduce the number of sessions of PE needs to be confirmed in a larger sample in the future.

Conclusions

In summary, the combination of PE and DPMAS is safe and effective in reducing the bilirubin level and improving blood coagulation in a small series of PALF due to mushroom poisoning. The combination of PE and DPMAS might serve as a bridge to transplantation or recovery.

Conflict of interest

The authors declare that they have no conflicts of interest.

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