Experience of Treatments of Amanita Phalloides-induced Fulminant Liver Failure with Molecular Adsorbent Recirculating System and Therapeutic Plasma Exchange

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Abstract

Objective: To evaluate the effects of molecular adsorbent recirculating system (MARS) and therapeutic plasma exchange (TPE) on patients with amanita phalloides-induced fulminant liver failure.

Material and Methods: We retrospectively analyzed nine cases of amanita phalloides poisoning where MARS and/or TPE was applied.

Results: The survival rate for the nine patients in this study was 66.7%. Patients who received both MARS and TPE therapies experienced higher survival rates than those who received MARS or TPE alone (100% vs 0%, 50%). A single session of TPE produced greater improvements in ALT (-58.6% vs -12.5%), AST (-44.2% vs -26.9%), total bilirubin (-44.4% vs -12.5%), and PT (-51.2% vs -4.89%) compared to a single session of MARS (all $p<0.05$).

Conclusion: The results suggest that TPE has better efficacy in removing toxins and improving liver functions. There is a trend that combined use of MARS and TPE may be more effective than either therapy alone, and early intervention may be more effective than delayed therapy. Additionally, the presence of severe hypoglycemia, severe liver failure, and renal failure indicated a worse outcome. *(JAEM 2014; 13: 181-6)*

Key words: Mushroom, fulminant liver failure, Amanita phalloides, molecular adsorbent recirculating system (MARS), therapeutic plasma exchange (TPE)

Introduction

Intoxication accidents due to eating wild mushrooms happen every year in many different regions of the world (1, 2). The clinical manifestations of mushroom poisoning vary based upon the species of mushroom, with the most severe cases and approximately 90% of fatalities, resulting from amatoxin-containing mushrooms, such as Amanita phalloides (3-7). Specifically, the consumption of amatoxin can cause severe liver damage, and in high doses, it can induce fulminant liver failure (FLF) (8). FLF is defined as sudden and severe liver dysfunction associated with jaundice and altered mental status (encephalopathy) in the absence of preexisting liver disease (9).

The primary treatment strategies are supportive measures, including gastric lavage, oral activated charcoal, fluid resuscitation, and targeted organ protections. Although there are no specific antidotes for amatoxin poisoning, in recent years, extracorporeal blood purification technologies, such as molecular adsorbent recirculating system (MARS), hemoperfusion, and therapeutic plasma exchange (TPE), have been used in clinical therapy (10). There is some evidence to show that MARS and/or TPE can remove toxins, bilirubin, bile acids, and inflammatory mediators and improve survival after hepatic encephalopathy (11-13). However, large-scale clinical trials have not been performed, and the extent to which these technologies avert the deleterious effects of amatoxins remains controversial (11). This aim of this retrospective study is to assess the effects of MARS and/or TPE on mushroom poisoning patients with severe liver failure.

Material and Methods

Patients

Mushroom poisoning patients from August 2011 to September 2013 were included. Patients aged less than 16 years or more

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Table 1. Demographic and clinical data of all patients

Baseline characteristics	1	2	3	4	5	6	7	8	9
Age	22	23	24	22	22	24	24	51	47
Gender	F	M	F	M	M	M	M	M	F
Onset time of symptoms (hrs)	10	11	10	10	11	11	10	12	12
Number of MARS sessions	1	0	1	0	1	4	3	1	1
Number of TPE sessions	0	2	1	1	0	1	1	3	3
Time from intoxication to MARS (hrs)	120		133		116	138	115	53	52
Time from intoxication to TPE (hrs)		114	113	122		121	117	69	68
Outcome	death	death	survival	survival	death	survival	survival	survival	survival

F: female, M: male

than 65 years old or who died with 24 hours after admission were excluded, and the remaining nine patients were included. All nine subjects had no significant past medical histories and had ingested multiple wild, white-colored mushrooms. The diagnosis of Amanita phalloides intoxication was established based upon the presence of classic amatoxin clinical manifestations and patient descriptions of the suspected mushroom. Permission for chart review was obtained from the ethical committee.

Routine Therapies

All patients received standard initial treatments, including gastric lavage, naso-duodenal tube with continual aspiration, multiple doses of activated charcoal, penicillin G, and vitamin K. Any patients who developed hypovolemia, hypoglycemia, electrolyte imbalances, metabolic acidosis, or coagulation disorders were treated with the appropriate supportive therapies.

Extracorporeal Blood Purification Management

In addition to these basic treatments, all patients received extracorporeal blood purification in the form of MARS and/or TPE. The criteria for extracorporeal purification to treat mushroom poisoning were based upon (a) a history of ingesting a white mushroom, (b) the typical symptoms (vomiting, epigastric abdominal pain, diarrhea) beginning 6 hours after mushroom ingestion, and (c) the presence of liver dysfunction (elevation of aminotransferases and/or bilirubin). The choice of MARS or TPE was based mainly on the availability of the machine at that time and the physician's proficiency and experience. Five patients received both MARS and TPE, two patients received only MARS, and two patients received only TPE.

A double-lumen tube was inserted into the femoral vein or the jugular vein to establish vascular access for MARS/TPE; unfractionated heparin was used as the anticoagulation drug. MARS was performed using the Teraklin machine (Teraklin, Rostock, Germany). Each MARS treatment lasted 6 hours. The blood flow rate was set to 150 ml/min, the albumin flow rate was set to 120 ml/min, and the dialysis flow rate was set to 1000 ml/hr. TPE was performed with the Fresenius Plasmaflu P2S machine (Fresenius Medical Care GmbH, Bad Homburg, Germany). Patients received calcium gluconate and promethazine before the treatment to help prevent allergic reactions. Each TPE treatment lasted for 2.5 hours and exchanged a total of 2500 ml of fresh plasma. The blood flow rate was set to 150 ml/min, and the plasma flow rate was set to 1000 ml/hr.

Measurements and Monitoring

Body temperature, heart rate, blood pressure, breath rate, and blood oxygen saturation were monitored during treatment in the ICU. Laboratory parameters, including serum electrolytes, glucose, globulin, albumin, prealbumin, blood urea nitrogen, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, total cholesterol, lactate dehydrogenase (LDH), creatine kinase (CK), α-hydroxybutyrate dehydrogenase (HBDH), prothrombin time (PT), activated partial thromboplastin time (APTT), internal normalized ratio (INR), fibrinogen, and complete blood count, were examined daily. Additionally, the model for end-stage liver disease (MELD) score was calculated to assess the severity of liver injury in the ICU. Hepatic encephalopathy (HE), a spectrum of neuropsychiatric abnormalities as a result of liver failure, was graded on a scale of 1-4 with the West Haven criteria, including the level of impairment of autonomy, changes in consciousness, intellectual function, behavior, and the dependence on therapy (14).

Statistical Analysis

Descriptive data are expressed as means±standard error (SE) or median (range). Analysis of variance and un-paired student's t-test were applied to compare the normally distributed variables. Mann-Whitney U-test was used to compare the non-normally distributed data. Categorical variables were expressed as proportions and compared using the chi-square test. The survival analysis was assessed by Kaplan-Meier statistics and compared using log-rank test. Statistical analysis was performed using SPSS 11.0 (SPSS Inc, Chicago, IL). A two-sided P value <0.05 was considered statistically significant.

Results

Overall Demographic Clinical Data

All nine patients developed acute gastroenteritis 10-12 hours following the ingestion. After 2-3 days, all patients presented with fatigue, anorexia, dull pain on the liver, jaundice, and abnormal laboratory indexes (elevated in liver enzymes, bilirubin, LDH, CK, and HBDH and lowered in fibrinogen, prothrombin activity, and total cholesterol). The demographic and clinical data of all patients are outlined in Table 1. Six patients developed hepatic encephalopathy within 3-5 days of ingestion; five of these patients deteriorated rapidly. Disseminated intravascular coagulation (DIC) presented in three patients, and three patients developed acute renal failure. Addition-

Table 2. The worst laboratory values for each patient observed during the hospital stay

Laboratory parameters	1	2	3	4	5	6	7	8	9
Platelets (×10^9/L) (normal: 100-300)	59	11	137	93	114	38	58	51	41
Creatinine (μmol/L) (53-108)	382	337	44	77	370	58	102	108	78
Ammonia (mmol/L) (11.2-58)	115.1	229.1	67.2	43.6	247	92	122	52.6	53.2
Total bilirubin (μmol/L) (1.7-17)	116.1	165.3	58.1	45.5	156.6	139.4	194	69.9	46.2
AST (U/L) (0-40)	3741	5700	4374	552	10,885	3497	3266	2582	2868
ALT (U/L) (0-40)	5684	8170	6720	1332	10,667	4717	6388	1741	2076
Albumin (g/L) (35-55)	27.6	27.7	29.3	31.3	35.8	31.1	33	25.3	29.9
Prealbumin (g/L) (0.28-0.36)	0.02	0.07	0.06	0.15	0.06	0.06	0.08	0.17	0.17
PT(s) (8.5-14.5)	>120	62.1	47.8	18.7	>120	59.2	61.3	29.9	31.7
INR (0.8-1.5)	>12	7.21	5.17	1.57	>12	6.79	7.09	2.79	2.99
LDH (U/L) (114-240)	4359	3478	859	505	3574	2750	1173	853	448
Glucose (mmol/L) (3.1-6.1)	0.88	1.9	6.92	6.1	0.7	4.53	4.89	4.7	4.7
Na+ (mmol/L) (135-145)	124	122	142	135	132	128	131	134	132
HBDH (U/L) (9-220)	1676	1474	472	267	1479	1159	1391	368	224
Total cholesterol (mmol/L) (3.5-6.1)	0.15	0.72	1.07	2.31	0.21	1.19	0.35	2.09	2.67
Creatine kinase (U/L) (25-200)	26097	753	41	800	458	403	182	157	139
Fibrinogen (g/L) (2-4)	0.00	0.62	0.30	1.42	0.86	1.29	1.51	1.17	1.28
Worst MELD score	54	51	29	15	62	36	39	25	22
Worst encephalopathy grade	4	4	1	0	4	3	4	0	0

ALT: alanine aminotransferase, AST: aspirate aminotransferase, PT: prothrombin time, INR: international normalized ratio, LDH: lactate dehydrogenase, HBDH: α-hydroxybutyrate dehydrogenase, MELD: The model for end-stage liver disease

ally, thrombocytopenia was present in seven patients, hypoglycemia was present in three patients, and one patient developed severe gastrointestinal bleeding. The most severe laboratory values for each patient are shown in Table 2.

The Effects of Extracorporeal Blood Purification

Five patients received both MARS and TPE therapies, two patients received only MARS, and two patients received only TPE.

A total of 12 MARS treatments were performed on seven patients. The MARS therapy had an immediate impact on several biochemical parameters (Table 3). ALT values decreased from pre-MARS levels by 16.1%, AST decreased by 26.9%, and total bilirubin decreased by 12.5% ($p<0.05$). In addition, MARS therapy was able to decrease the heart rate (HR) by 7.1% ($p<0.05$). MARS had no significant influence on PT, fibrinogen, white blood cell counts (WBC), mean arterial pressure (MAP), albumin, prealbumin, or platelet levels ($p>0.05$); however, MARS did induce a slight decrease in hemoglobin (Hb) (4.8%, $p<0.05$).

A total of 12 TPEs were performed on seven patients. ALT levels improved sharply after TPE (3377.4±628.4 pre-TPE vs 1399.3±209.8 U/L post-TPE). Similarly, AST values (1925.7±416.2 pre-TPE vs 1074.4±300.5 U/L post-TPE), total bilirubin levels (102.6±10.3 pre-TPE vs 89.8±10.3 μmol/L post-TPE), and PT values improved (-42.28±8.47 pre-TPE vs -20.64±0.61s post-TPE) (all $p<0.05$) (Table 4). TPE did not cause a noticeable effect on HR, MAP, WBC, prealbumin, and fibrinogen; however, TPE did decrease Hb (-13.8%), albumin, and platelet levels (-24.9%) ($p<0.05$). Compared with MARS, TPE caused greater improvements in (-58.6%, vs -16.1%, $p<0.05$), AST (-44.2% vs -26.9%), total bilirubin (- 44.4% vs -12.5%, $p<0.05$), and PT (-51.2% vs -4.89%, $p<0.05$).

Table 3. Changes of laboratory parameters before and after MARS (mean±SE)

n=12	**Pre-MARS**	**Post-MARS**	**p**
ALT (U/L)	2572.7±616.1	2158.5±545.0	0.042
AST (U/L)	1254.3±416.0	917.4±309.8	0.026
Total bilirubin (μmol/L)	102.6±10.3	89.8± 10.3	0.014
PT (s)	40.93±10.76	38.58±8.89	0.518
HR (beats/min)	91.67±8.47	85.17±8.43	0.042
MAP (mm Hg)	80.73±4.14	84.39±3.29	0.408
Fibrinogen (g/L)	1.64±0.16	1.48±0.18	0.056
WBC (×10^{12}/L)	9.87±1.38	9.38±1.15	0.516
Hemoglobin (g/L)	124.0±6.3	118.2±6.4	0.043
Platelet (10^9/L)	116.9±24.5	106.7±21.3	0.132
Albumin (g/L)	36.25±1.44	38.11±1.19	0.067
Prealbumin (g/L)	0.134±0.027	0.134±0.033	1

ALT: alanine aminotransferase, AST: aspirate aminotransferase, PT: prothrombin time, HR: heart rate, MAP: mean arterial pressure, WBC: white blood cell

Six of the nine patients (66.7%) in this study survived amatoxin poisoning. All five patients who received both MARS and TPE survived, half of the patients (n=2) who received only TPE survived, and

Table 4. Changes of laboratory parameters before and after TPE (mean±SE)

n=12	Pre-TPE	Post-TPE	p
ALT (u/L)	3377.4±628.4	1399.3±209.8	0.001
AST (U/L)	1925.7±416.2	1074.4±300.5	<0.001
Total bilirubin (μmol/L)	86.87±16.44	48.29±8.03	0.001
PT (s)	42.28±8.47	20.64±0.61	0.023
HR (beats/min)	84.92±7.63	84.50±5.72	0.912
MAP (mm Hg)	87.14±2.74	85.12±3.86	0.510
Fibrinogen (g/L)	1.65±0.09	1.45±0.07	0.152
WBC (×1012/L)	4.95±0.51	4.78±0.43	0.354
Hemoglobin (g/L)	138.67±5.12	119.58±5.27	0.001
Platelet (×109/L)	121.08±20.27	90.92±15.71	0.003
Albumin (g/L)	35.99±1.05	32.15±0.71	<0.001
Prealbumin (g/L)	0.160±0.19	0.177±0.014	0.122

ALT: alanine aminotransferase, AST: aspirate aminotransferase, PT: prothrombin time, HR: heart rate, MAP: mean arterial pressure, WBC: white blood cell

Table 5. Comparisons of clinical characteristics of survivors and non-survivors

Characteristics	Non-survivors (n=3) Median (Range)	Survivors (n=6) Median (Range)	P value
Platelet (109/L)	59 (11-114)	54.5 (38-137)	1
LDH (U/L)	3574 (3478-4359)	679 (448-2750)	0.024
Creatine kinase (U/L)	753 (458-26097)	169.5 (41-800)	0.095
Creatinine (μmol/L)	370 (337-382)	77.5 (44-108)	0.024
ALT (U/L)	8170 (5684-10667)	3792.5 (1332-6720)	0.095
PT (s)	120 (62.1-120)	39.75 (18.7-62.1)	0.024
AST (U/L)	5700 (3741-10885)	2671 (552-4374)	0.048
Total bilirubin (μmol/L)	156.6 (116.1-165.3)	64 (45.5-194)	0.262
Ammonia (mmol/L)	229.1 (115.1-247)	60.2 (43.6-122)	0.048
Total cholesterol (mmol/L)	0.21 (0.15-0.72)	1.64 (0.35-2.67)	0.048
Albumin (g/L)	27.7 (27.6-35.8)	30.5 (25.3-33)	0.905
Prealbumin (g/L)	0.06 (0.02-0.07)	0.115 (0.06-0.17)	0.167
Fibrinogen (g/L)	0.62 (0-0.86)	1.285 (0.3-1.42)	0.095
Glucose (mmol/L)	0.88 (0.7-1.9)	4.795 (4.53-6.92)	0.024
HBDH (U/L)	1478.9 (1473.5-1676.1)	419.95 (224-1391.1)	0.024

ALT: alanine aminotransferase, AST: aspirate aminotransferase, PT: prothrombin time, LDH: lactate dehydrogenase, HBDH: α-hydroxybutyrate dehydrogenase

none of the patients (n=2) who received only MARS survived. Of the three non-survivors, two died 6 days after and one died 8 days after ingesting toxic mushrooms.

Clinical Parameters to Predict Outcomes

There were statistically significantly differences between AST, LDH, creatinine, PT, glucose, ammonia, and HBDH in survivors and non-survivors ($p<0.05$). Of these parameters, the largest changes were in PT, ammonia, creatinine, glucose, and HBDH. There were no significant differences in laboratory values between survivors and non-survivors for any other parameters. The demographic and clinical characteristics of survivors and non-survivors are presented in Table 5.

Complications from Blood Purification

One patient suffered a slight allergic reaction during TPE therapy. Additionally, TPE therapy resulted in decreased Hb values, albumin value, and platelet counts, but they remained within acceptable physiologic ranges (Tables 2 & 3). MARS therapy also caused a slight drop in Hb. No other serious adverse effects were observed following blood purification treatments.

Discussion

Our study demonstrates that either MARS or TPE could diminish liver injuries induced by amatoxin-containing mushroom intoxication. TPE therapy resulted immediately in greater improvement in liver function as compared to MARS therapy. There is a trend that combined TPE and MARS therapy was more effective at ameliorating amatoxin poisoning than either therapy alone. This study also found evidence to suggest that severe hypoglycemia, severe liver injury (very low PT and very high ammonia), and severe renal injury (very high creatinine) can predict mortality from amatoxin poisoning.

Amatoxins cannot be destroyed by heat (15). The liver is recognized as the target organ for Amanita phalloides toxins. The overall severity of the intoxication depends on the amount of toxin ingested and the time elapsed between ingestion and initiation of treatment. The lethal dose of amatoxin is very low (5, 15). In this study, liver injury began approximately 24 hours after ingestion and progressed into FLF approximately 72 hours after consumption.

Treatment of poisoning patients requires the rapid and effective elimination of the toxin and its potentially toxic metabolites. Several studies have suggested that early hemoperfusion (<24 hours after exposure) over a charcoal filter is effective in averting the deleterious effects of amatoxins and should be considered (16). Hemodialysis may also be used; however, because of the rapid time course of the absorption and excretion of amatoxins, hemodialysis will have a limited effect, even if applied 24 hours after consumption (17-18). MARS is a modified dialytic method that mimics the biological features of the hepatocyte membrane. MARS is capable of transferring protein-bound and water-soluble toxic metabolites from the bloodstream into a dialysate compartment via a special membrane (19), effectively functioning as an artificial liver for acute liver failure induced by poisoning.

Treatment with MARS has recently been described as an effective homeostatic tool in FLF (20, 21). There are several case reports using MARS in the treatment of FLF secondary to mushroom poisoning in both children and adults, and for the vast majority of these patients, MARS successfully improved symptoms and biological parameters following liver damage (22, 23). Additionally, all mushroom-poisoned patients in the MARS group of the Helsinki study survived despite late treatment and the presence of severe liver failure (24). Therefore, the beneficial effect of MARS was most likely related to the artificial restoration of liver function, not toxin elimination.

TPE, another traditional extracorporeal purification method, is more widely available (25), especially for the removal of toxic sub-

stances (13). At present, plasmapheresis is used successfully in the treatment of phalloid mushroom intoxications (12, 25). Our report showed that TPE produced greater liver function improvements than MARS. TPE could improve PT, but MARS could not. The possible explanation is that TPE works through direct plasma exchange and removes the toxins immediately. Coagulation factors are also replenished during TPE, which helps to improve the coagulation functions. Whether TPE is superior to other purifications is unknown, as the current literature lacks such comparisons. At least, we tend to prefer TPE in urgent conditions due to its better immediate effects.

An interesting discovery is that all five patients who received both MARS and TPE survived, but the power was too small to come to a conclusion. MARS appears to replace liver function, and TPE appears to remove endogenous toxins. Determining whether it will be better to use a combination of MARS and TPE will require more studies.

It is generally accepted that extracorporeal decontamination treatment is more useful if started very early (26). From our data, the worst peak values of liver function parameters happened from the 4th to 6th day. The first seven patients were transferred to the ICU on the fifth or sixth day after ingestion, three of whom died despite blood purification. It appeared as though the disease progressed too far for blood purification. The final two patients received MARS and TPE on the 3rd day after ingestion and survived. Taru Kantola recommended initiating MARS within 3 days following ingestion, because encephalopathy or other serious complications had not developed yet in most patients (26). Therefore, we recommend that MARS/TPE treatment should be initiated as early as possible.

There were significant differences between glucose, AST, PT, creatinine, ammonia, and HBDH in survivors and non-survivors. The differences between glucose, PT, ammonia, and creatinine were much greater, and they were associated with a poor outcome after amatoxin intoxication. The hypoglycemia was most likely the result of impaired hepatic gluconeogenesis, increased insulin release, and tissue destruction in the pancreas (27). The persistent increase in ammonia and decrease of PT indicate refractory liver failure, and high levels of creatinine suggest severe kidney injury. All of these complications predicted a worse outcome.

Study Limitations

There are several limitations with this study. This was not a randomized clinical trial, and the small sample size limited the power of our findings. Additional randomized, case-controlled studies with a larger patient population are needed to assess the efficacy of MARS and TPE. However, this report provides preliminary data for further clinical trials.

Conclusion

Both MARS and TPE were demonstrated to remove toxins and improve liver functions measured by laboratory parameters, but TPE had better efficacy. Our data also suggest that these therapies are more efficacious when provided early. Additionally, hypoglycemia; low PT; and high LDH, AST, creatinine, and ammonia all represent negative prognostic markers. Although these findings are promising, additional case-controlled, randomized studies are required to confirm our results.

Ethics Committee Approval: Ethics committee approval was obtained from the local ethics committee.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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