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Original Article

From Activated Charcoal to Selective Plasma Exchange: A Retrospective Analysis of Mushroom Poisoning Cases Treated in The Intensive Care Unit

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Abstract

Background This study aims to evaluate the treatment modalities of adult patients presenting with mushroom poisoning treated in the intensive care unit (ICU) with special consideration of extracorporeal liver support systems.

Material and Methods Records of patients with mushroom poisoning treated in the ICU between January 2007 and December 2014 were analyzed retrospectively.

Results Sixteen adult patients were treated in the ICU for mushroom poisoning during the designated study period. Average time from ingestion of mushrooms to first symptoms was 17.81 hours, and to ICU admission was 2.38 days. In cases with elevated liver transaminases, penicillin G, silibinin and N-acetyl cysteine were used. Extracorporeal support systems were used for detoxification and as a bridge to liver transplantation in 9 cases. Of these, 4 were plasmapheresis, 3 were selective plasma exchange, 1 was hemoperfusion and 1 was direct adsorption from plasma. Two cases underwent emergency liver transplantation.

Conclusions Liver transplantation is the most definitive and effective treatment in indicated cases of mushroom poisoning. Extracorporeal support systems should be considered in the early period both as a treatment modality on their own or to save time until the definitive treatment is possible. The question of which extracorporeal detoxification technique to use is difficult to answer and controlled clinical trials which compare their efficacy are needed.

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Introduction

Mushroom poisoning poses an important public health problem worldwide. There are around 5,000 species of mushroom, of which around 3% are responsible for poisoning.[1,2] Turkey is rich in terms of the mushroom flora. They are consumed widely in the spring and autumn seasons which accounts for the increased number of poisonings seen at this time.[3,4] The clinical presentation depends on the type of mushroom ingested. Generally, mushroom poisoning presents a wide range of symptoms from nausea, vomiting, abdominal pain and diarrhea to symptoms of full-blown acute liver failure.[1,4]

The treatment of mushroom poisoning begins in the emergency department where the patients first present, and usually continues into the intensive care unit (ICU). The first step in treatment is provision of supportive measures (fluid resuscitation, correction of electrolyte imbalances, etc.), after which gastric lavage and repetitive doses of activated charcoal can be used.[5] Poisoning with the *Amanita phalloides* species especially leads to kidney and liver dysfunction. Although treatments such as silibinin, high dose penicillin-G, N-acetyl cysteine (NAC) and extracorporeal support systems are effective when commenced promptly; in cases of fulminant liver failure, liver transplantation (LT) is the only acceptable treatment modality.[5,6]

Many extracorporeal methods of toxin removal (hemoperfusion, plasma exchange) are used, but they seem to be effective only at the initial stage of poisoning (up to 48 hours after ingestion).[7] Therefore, early diagnosis and aggressive treatment of mushroom poisoning, as well as prompt transfer to a transplantation center can be regarded as life-saving for this condition. The expanding use of liver support systems and experience with LT makes these cases increasingly worthy of close follow-up.[6,7]

This study aims to evaluate the medical and extracorporeal treatment modalities, the need for LT and outcomes of treatment in the ICU for adult patients presenting with mushroom poisoning.

Material and Methods

The institutional Medical Ethics committee granted ethical permission for the conduction of this study. Records of adult (18 years-old) patients who required treatment for mushroom poisoning in ICU between January 2007 and December 2014 were retrospectively analyzed.

The following parameters were recorded for each patient: age, sex, presenting signs and symptoms and time of commencement, various scores for predicting morbidity and mortality (Acute Physiology and Chronic Health Evaluation [APACHE] II and Sequential Organ Failure Assessment [SOFA]), treated organ failures, Model for End-Stage Liver Disease (MELD) scores of those who developed liver failure, treatments applied (medical, extracorporeal or liver transplantation), laboratory findings, length of stay in the ICU, and results of treatments.

Statistical analysis was conducted using the "Statistical Package for the Social Sciences- SPSS 22.0" program. Categorical variables are expressed as percentage (%) and continuous variables are expressed as mean±standard deviation (mean±SD).

Results

Seventeen adult patients were treated in the ICU for mushroom poisoning during the designated study period. Demographic properties, ICU scores and properties specific to their mushroom poisoning are presented in Table 1.

The most common pathological laboratory finding during ICU admission was elevation of liver transaminases (n:12). Specific laboratory findings and values are presented in Table 2.

Eight cases (50%) required mechanical ventilation therapy and 6 cases (37.5%) required inotropic and vasopressor agents in the ICU. Nine cases (56.25%) developed acute liver failure (ALF). The average MELD score for these patients was 29.96±9.12. The lactate levels for one of these patients could not be found. The average lactate level for the remaining 8 patients was 101.92±92.07 mg/dL (min-max: 20.1-290.09 mg/dL). MELD scores and laboratory findings of patients who developed ALF in the ICU are summarized in Table 3.

A review of treatment modalities revealed that the most commonly used modality was repetitive doses of activated charcoal which was used in 10 cases (62.5%). In cases with elevated liver transaminases, silibinin, N-acetyl cysteine (NAC) and penicillin G was used for hepatoprotective

Table 1. Baseline characteristics of the patients.

Age (years) (mean±SD)	55.38±17.42
Sex [n (%)]	
Female	10 (62.5)
Male	6 (37.5)
Month of presentation [n (%)]	
May	1 (6.3)
June	3 (18.8)
October	10 (62.5)
November	1 (6.3)
December	1 (6.3)
Time from ingestion to first symptom [n (%)]	
<6 hours	2 (12.5)
>6 hours	14 (87.5)
Time from ingestion to ICU admission (days) (mean±SD)	2.38±1.41
ICU scores (mean±SD)	
APACHE II	13.44±7.22
SOFA	4.13±4.52
Presenting symptoms [n (%)]	
Nausea	16 (100)
Vomiting	15 (93.8)
Diarrhea	10 (62.5)
Alteration of consciousness	5 (31.3)
Abdominal pain	4 (25)
Hallucination	1 (6.3)
Hematuria	1 (6.3)

ICU: Intensive Care Unit; APACHE: Acute Physiology and Chronic Health Evaluation; SO Sequential Organ Failure Assessment.

purposes. Extracorporeal support systems were used for detoxification and as a bridge to liver transplantation in 9 cases. Of these, 1 was hemoperfusion (HP) (6.3%), 1 was direct adsorption from plasma (6.3%) (Fractioned Plasma Separation and Adsorption [FPSA], Prometheus®, Fresenius Medical Care, Germany), 4 were plasmapheresis (25%), and 3 were selective plasma exchange (SPE) (18.8%) (Evaclio™, Plasauto, Germany). Treatments applied in all patients are summarized in Table 4.

Two cases (12.5%) underwent successful emergency LT due to development of ALF. These patients had received SPE before transplantation. One patient developed brain death during ICU stay. The average length of ICU stay was 5.13±6.14 days and 6 cases (37.5%) died despite treatment.

Table 2. Laboratory parameters of the patients.

Laboratory parameters	Admission to ICU (n:16)	24 hours after admission to ICU (n:15)*	Last recorded (n:16)	Normal Ranges
AST (U/L)	2126.2±3352.1	2050.0±3335.5	1049.94±296.6	11-25
ALT (U/L)	674.1±1739.0	1674.1±1739	349.00±51.72	7-28
Ammonia (µg/dL)	213.1±274.1	198.3±146.1	133.83±104.60	31-123
INR	2.6±2.2	2.6±2.5	1.51±0.61	0.85-1.15
Total bilirubin (mg/dL)	2.4±1.6	2.4±1.6	3.21±4.67	0.2-1.2
Direct bilirubin (mg/dL)	1.3±1.1	1.4±0.99	1.81±2.75	0.0-0.5
Urea (mg/dL)	57.0±41.5	38.0±34.7	40.31±38.4	15-45
Creatinine (mg/dL)	1.2±0.94	0.99±0.56	1.34±1.04	0.56-0.85
Blood glucose (mg/dL)	120.4±39.5	124.4±54.2	121.38±65.88	70-100

AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; INR: International normalized ratio for prothrombin time. Results are expressed as mean ± SD.
*One patient died within first 24 hours.

Discussion

Mushroom poisoning is a health problem in many countries resulting in both morbidity and mortality.[5] The difficulties related to the management of patients depend mostly on the type of ingested mushroom and the patient's symptoms. Although mostly results in mild to moderate cases of gastroenteritis which are usually self-limiting, poisoning with *Amanita phalloides* results in 90% mortality and even minimal amounts of ingestion can result in death.[8,9] The possibility of A. phalloides should be considered, especially in cases where type analysis cannot be made in the laboratory.[5,9]

The most basic steps in the treatment of mushroom poisoning are early hospitalization, IV fluid resuscitation, and supportive and symptomatic treatment. Since there is no antidote for mushroom poisoning, some medications such as silibinin, NAC, penicillin G and cimetidine can be used for hepatoprotective purposes, especially for amatoxin poisoning.[10,11] Silibinin prevents amanitin from binding to the hepatocyte membrane and entering the cell.[6,12] NAC removes free oxygen radicals from the environment and thereby reduces hepatocyte damage, and in addition to its minimal side effects, accounts for its reason for use in mushroom poisoning.[13] Penicillin G reduced uptake of amanitin by hepatocytes and thereby protects hepatocytes.[14] Conducted studies support the use of multitherapy rather than monotherapy with these drugs.[5,12,14] Nine cases in our study were treated with a combination of these drugs.

One of the most serious consequences of mushroom poisoning is acute liver failure. Extracorporeal liver support systems can be used to remove toxins as well as to act as a bridge to LT in those cases that are suitable.[7] Hemoperfusion, FPSA, plasmapheresis and SPE are major extracorporeal detoxification methods used in mushroom poisoning. Sometimes, they allow time for regeneration of liver tissue, thereby removing the need for transplantation.[7,15]

Hemoperfusion has been used in amatoxin poisonings since 1978 and is more effective when commenced in the first 24 hours after ingestion.[16] Amatoxins do not bind to proteins circulate and freely in serum. They also possess a relatively small molecular weight (around 900 Da) and have a high affinity for charcoal and polymers used in conduction of HP.[16] In FPSA the patient's plasma is separated with the use of membrane with a molecular permeability of 250 kDa and then passed through 2 columns with different adsorbents. Water soluble substances, on the other hand, can be removed through high flow dialysis of blood directly in circulation.[17] Bergis et al.[17] reported the successful use of FPSA until the urinary amatoxin level reached nil in 9 of 20 patients. Plasmapheresis involves the clearance of large molecular weighted substances and protein bound molecules with a small volume

Table 3. MELD scores and laboratory results of patients treated for acute live failure*

	MELD	Encephalopathy**	Lactate (mg/dL)	INR	AST (U/L)	ALT (U/L)
Case 1	40.7	2	20.1	8.9	>4202	>4113
Case 2	28.09	3	46.3	6.6	259	483
Case 3	14.6	4	53.5	3.07	613	1562
Case 4	33.02	3	158	3.0	12804	2621
Case 5	26.8	None	25	3.4	5670	4130
Case 6	18.08	None	76	3.02	4318	4575
Case 7	15.41	2	147	2.1	1008	667
Case 8	33.7	3	290.09	2.6	1940	1654
Case 9	32.27	4	Missing data	2.6	254	159

MELD: Model for End-Stage Liver Disease; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; LDH: Lactate Dehydrogenase; INR: International Normalized Ratio for prothrombin time.
*Highest values during follow-up. **West Haven Criteria for Encephalopathy
Reference values: Lactate: 0-20 mg/dL, AST: 11-25 U/L, ALT: 7-28 U/L, INR: 0.85-1.15.

of distribution from plasma and consequent replacement with appropriate IV fluids.[18,19] It is important to note the low mortality rates achieved through the use of conservative treatment in combination with plasmapheresis especially when commenced in the first 36 hours.[18-20] The mechanism for SPE involves the use of a filter for the removal of substances in plasma according to their molecular size. Hemofiltration and plasma exchange can occur concurrently according to the filter used. There are studies reporting that SPE increases survival in patients with ALF. Unlike conventional plasma exchange, in SPE, coagulation proteins are not removed.[21,22]

In our study, extracorporeal support systems were used in 9 cases. In one patient HP was used 5 times and a positive result to treatment was observed. Fractioned plasma separation and adsorption was used in one patient on the 7th day after ingestion but the patient died due to multiorgan failure. The fact that the patient was admitted to the ICU on the 5th day after ingestion and that the FPSA was initiated in the late period was probably the reason for failure. Plasmapheresis was used unsuccessfully in 4 patients and these patients died at the end of treatment, most probably because these patients were admitted to the ICU after the first 36 hours (48-120 hr.) after ingestion and only then could plasmapheresis be administered. Three patients underwent SPE. Two cases of them proceeded to undergo LT, whereas 1 patient was able to be treated without LT.

Table 4. Treatments applied for patients with mushroom poisoning.

Patient	Year of Presentation	Acute Liver Failure	Drugs	Extracorporeal Treatment	Outcome
Case 1	2007	Yes	IV hydration*	-	Died
Case 2	2008	Yes	Silibinin	FPSA	Died
Case 3	2009	No	Activated charcoal	-	Survived
Case 4	2009	Yes	Activated charcoal	Plasmapheresis	Died
Case 5	2009	No	Activated charcoal	-	Survived
Case 6	2010	No	Silibinin, penicillin	-	Survived
Case 7	2010	Yes	Activated charcoal, silibinin, penicillin	Plasmapheresis	Died
Case 8	2010	No	Activated charcoal	-	Survived
Case 9	2010	Yes	Silibinin, penicillin, NAC	Hemoperfusion	Survived
Case 10	2010	No	Activated charcoal, penicillin	-	Survived
Case 11	2012	Yes	Silibinin, penicillin, NAC	Plasmapheresis	Died
Case 12	2014	Yes	Silibinin, penicillin	Plasmapheresis	Died
Case 13	2014	No	Activated charcoal	-	Survived
Case 14	2014	Yes	Activated charcoal, silibinin, penicillin, NAC	SPE	Liver transplantation-Survived
Case 15	2014	Yes	Activated charcoal, silibinin, penicillin, NAC	SPE	Liver transplantation-Survived
Case 16	2014	No	Activated charcoal, silibinin, penicillin, NAC	SPE	Survived

FPSA: Fractioned Plasma Separation and Adsorption, **NAC:** N-acetyl cysteine; **SPE:** Selective plasma exchange;
*Patient was in multiorgan failure when admitted to ICU and died before any specific treatment was begun; Brain death.

There are studies present which report the successful use of molecular adsorbent recirculating system (MARS) in patients with ALF due to amatoxin ingestion, either as a bridge to LT or as a treatment modality on its own.[23] This method is an extracorporeal system which uses a closed circuit to allow for the dialysis of protein bound and water-soluble substances in the plasma using albumin.[23,24] We were unable to use MARS due to technical reasons.

The use of extracorporeal systems to remove toxins from circulation has increased in the last 30 years.[20] The mortality rates reported in studies which used extracorporeal systems are significantly lower than those studies in which conservative approaches were preferred.[20,22-24] The question of which detoxification technique to use is one that is difficult to answer as there are no controlled clinical trials which compare their efficacy. The early (with 36 hours of ingestion) use of the method chosen for detoxification, as well as the clinical and laboratory follow-up and measurement of toxin levels in bodily fluids is essential in determining the duration and repetition of application, as well as in ensuring its success.[7,18,22]

The limitations of our study include the fact that it is retrospective with a limited amount of cases from a single center. Although mushroom poisonings are actually encountered more commonly than those reported here, we aimed to give place only to those cases which required ICU admission. Also, due to technical reasons mushroom typing was not possible.

Consequently, early recognition and treatment are essential in decreasing morbidity and mortality from mushroom poisonings. Acute or fulminant liver failure is characterized . by clinical findings accompanying a sudden total or near total deterioration of liver function. Its definitive treatment is LT. The use of extracorporeal methods as organ support systems can extend the time until transplantation is possible, as well as ameliorating the clinical condition of the patient. Further randomized controlled trials are needed to put forth the net effects of extracorporeal liver support systems. Nevertheless, we believe that these modalities should be considered and used more often for the treatment of such patients in the ICU.

Conflict of interest

All authors declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; any other relationships or activities that could appear to have influenced the submitted work.

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