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Early Hydration Therapy in Mushroom Poisoning Improves Mortality and Morbidity

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ABSTRACT

Background: Mushroom poisoning is frequently encountered in Upper Assam causing significant mortality and morbidity.

Aim & Objectives: This study was undertaken as a prospective case-control study comparing patients treated with early hydration and patients treated symptomatically with normal standard of care to study the effect of early hydration therapy on the mortality and morbidity.

Materials and Methods: All the patients of mushroom poisoning were given three to four litres of intravenous fluid per 24 hours unless signs of volume overload were seen. Continuous nasogastric aspiration was instituted. Other standard of care included Silimarin, N-acetylcysteine,Penicillin G and Vitamin C.They were compared with our old cohort of patient whose complete clinical records were available in our institute.

Results: We studied 94 cases of mushroom (39.4% male and 60.6% female). 13 (13.8%) patients expired. Loose stool (94.7%), vomiting (80.9%) and pain abdomen (72.3%) were the most common symptoms in mushroom poisoning patients overall. Icterus and neurological manifestation were common. When we compared these 94 cases with our old cohort of 48 patients, we noticed significant mortality benefit (13.8% vs 43.7%). Hypovolemic shock was only 2.13% in comparison to 22.9%. Acute liver failure, acute kidney injury and bleeding manifestations were 39.36%, 9.57% and 3.19% respectively in comparison to 64.58%, 27% and 14.58% respectively in those who were treated only symptomatically. The Odds ratio of acute liver failure was 0.356 and acute kidney injury was 0.285.

Conclusion: Early hydration therapy and nasogastric aspiration of bile significantly reduces the mortality and morbidity in patients presenting with signs and symptoms of mushroom poisoning.

INTRODUCTION

Mushroom poisoning is a rare condition occurring in very specific geographic locations around the globe, mostly near tropical rainforests during humid and monsoon seasons.There are approximately 100 poisonous mushroom species out of approximately 5000 species. Out of these 100 poisonous species only about 32 species have been associated with fatalities.[1]Greater than 90% of cases of fatal poisoning are caused by ***Amanita phylloides***(death cap) or ***Amanita verna*** (destroying angle).[1]Mushroom poisonings has been frequently encountered in upper part of Assam of north east India and are often referred to our tertiary care center and has caused significant mortality and morbidity.[2,3] There are no universally accepted guidelines to treat mushroom poisoning, though various medications have been tried. Enjalbert F et al. in 2002 reviewed 2108 hospitalized amatoxin poisoning exposures as reported in the medical literature from North America and Europe over the last 20 years and concluded that benzylpenicillin (Penicillin G) alone and in association was the most frequently utilized chemotherapy.But this treatment showed little efficacy. Thioctic acid and steroids showed no benefit. Silybin, administered either as mono-chemotherapy or in drug combination and N-acetylcysteine as mono-chemotherapy may have some beneficial role.[4]Das AK has noted that amatoxin is the most common poison encountered in our center andabout 35 mushroom species in three genera (Amanita, Galerina, and Lepiota) contain amatoxin.[5] The most important fact is that the fatality rate for Amanitin poisoning is about 50% without prompt, knowledgeable medical treatment.[5] In our previous 2013 publications on mushroom poisoning patients coming to our institute, we found very high(43.75% (21/48)) mortality.[2]Those patients were given normal standard of care as per available review of literature by Das AK,[5] who also noted that a need to develop our own treatment protocol was important to reduce the mortality and morbidity of mushroom poisoning cases coming to our institute for referral. In 2013, we also noted significant benefit for patients who received forced diuresis [2].. Todd Mitchell MD, the Principal Investigator of an amatoxin mushroom poisoning Clinical Trial in the USA using intravenous silibinin, assisted with the management of several cases of amatoxin mushroom poisoning in North Lakhimpur, Assam in 2011 [6]. Dr. Mitchell assisted us with his views in April 2014 and was invited to present at AMCH the following month**.**. We found his emphasis on aggressive IV fluid hydration to be particularly helpful and in agreement with our previous observation of reduced mortality among those who received forced diuresis and Das AK's[5] aggressive management of fluid losses. Consistent with our 2013 data, we observed that patients who received early IV hydration appeared to have better ***outcomes in terms of mortality, so in April 2014 we*** adjusted our standard hospital protocol to include early IV hydration for all future cases of mushroom poisoning. This paper describes a prospective case-control study comparing mushroom poisoning treated with early rehydration with our previous cohort of patients treated symptomatically with the previous conventional standard of care, to study the effect of early hydration therapy in patients with mushroom poisoning coming to our tertiary care hospital on the mortality and morbidity.

MATERIALS AND METHODS

All the patients presenting to our hospital with mushroom poisoning after April 2014 till April 2016 were included in our prospective study. Proper clinical and diet history including amount, type and procedure of cooking of mushroom was taken. Clinical examination was done and laboratory test were performed during and after admission at frequent intervals. Serum Blilirubin and fraction was done in all cases of acute liver failure by modified Jendrassik and Grof method,[7] Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) were done by IFCC kinetic method,[8,9]Alkaline Phosphatase was done by pNPP kinetic method,[10] Gamma GlutamulTranspeptidase was done by IFCC kinetic method[7] and Serum creatinine was done by Jaffe method[11] in the instrument Siemens Dimension RxLautoanalyzer. All these patients were given three to four litres per 24 hours mostly ringers lactate and normal saline. Regular monitoring of vitals like blood pressure, pulse, respiratory rate, urine output and auscultation of chest was done. If any patient was found to have signs and symptoms of volume overload or pulmonary oedema, intravenous fluid was reduced and diuretics were added. Nasogastric (Ryles) tube was placed and they were kept nil orally for 48 to 72 hours. Regular aspiration of Ryles tube was done to remove any bilious material. They were restarted with small oral liquid diets after 48 to 36 hours if the liver and renal function tests improve. In seriously ill patients intravenous fluids were continued and dextrose infusion was added. They also received the standard of care which included 15 to

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20 ml of Silimarin (Silybonsyp) thrice daily by ryles tube and intravenous N-acetylcysteinewas given as a loading dose of 100 mg/Kg over 6 hours followed by 6.25 mg/Kg/hr to continue for 48 to 72 hr or till improvement. In seriously ill patients intramuscular Penicillin G was given in a dose of 1.2 million units once daily. Vitamin C tablets were crushed and given via ryles tube diluted with water thrice daily and oral vitamin C tablets were added when the patient was allowed to take orally. Their improvement was monitored daily and recorded. They were compared with cohort of patientsof our previous observational study in 2013 whose complete clinical records were available in our institute.[2] Ethical clearance was obtained from Assam Medical College Ethics Committee before starting the study. Informed consent was taken from all the patients and/or their attendants before enrolling them in the study. Statistical Analysis was done by chi-square test using Epi Info™ software version 7.2.2.1.

RESULTS

We studied 94 cases of mushroom poisonings presenting to our Assam Medical College and hospital in from April 2014 till April 2015. 37 (39.4%) patients were male and 57 (60.6%) were female. 13 (13.8%) patients expired, including 8 (21.6%) male and 5 (8.8%) female. The patients came in three clusters, one during April-May 2014 (69 patients), another during August 2014 (5 patients) and during April 2015 (20 patients). Loose stool (94.7%), vomiting (80.9%) and pain abdomen (72.3%) were the most common symptoms in our patients. Icterus was present in half of the total patients and neurological manifestation was seen in one-fourth of the cases. Uremia was seen in nine cases and bleeding manifestations was seen in three cases. All these complications were significantly higher in patients who expired (Table 1). The Laboratory parameters of fatal cases show a higher level of liver enzymes (AST and ALT) , serum creatinine and Prothrombin time. (Table 2) When we compared the clinical findings of these 94 patients of mushroom poisoning with our previous cohort of 48 patients (Control) who were treated symptomatically without much emphasis on early hydration, we noticed significant mortality benefit (13.8% vs 43.7%). Hypovolemic shock was only 2.13% in patients treated with early hydration in comparison to 22.9% in those treated conventionally. The number of patients with acute liver failure, acute kidney injury and bleeding manifestations were 39.36%, 9.57% and 3.19% respectively in those who were treated with early hydration; whereas the same was significantly higher (64.58%, 27% and 14.58% respectively) in those who were treated only symptomatically. The Odds ratio of acute liver failure was 0.356CI 95% (p value 0.0044) and acute kidney injury was 0.285CI 95% (p value 0.0064). This indicated that early hydration therapy in mushroom poisoning cases could significantly reduce the hepatic and renal injury. The Odds ratio for mortality was 0.2063 CI 95% (p value <0.001) indicating that four out of five cases of mushroom poisoning cases can be saved by initiating early hydration therapy. The Odds ratio for hypovolemic shock and bleeding manifestations was also very low, 0.073 CI 95% (p value <0.001) and 0.193 CI 95% (p value 0.0121) respectively showing the reduced morbidity achieved with early hydration therapy (Table 3).

DISCUSSION

BarthakurB noted that consumption of wild mushroom is an age-old habit amongthe different tea garden communities and a vast tribalpopulation of Assam.[12]A number of sites in different tea garden areas of Assam, which are predominantly inhabited by labourers had reported nearly 30 deaths due to mushroom poisoning and deadly poisonous fungi belonging to the group of Amanita do not produce noticeable symptoms until eight to twelve hours after injestion.[12]This delay in symptoms may be the primary reason for delayed presentation and high mortality. Sharma J et al. and our studies have also reported many mushroom poisoning deaths due to amatoxin poisoning.[2,3]The mortality in our studies were much higher than studies reported from the west (Table 4). [13,14] Eren SH et al.[13] from Turkey studied 294 patients (173 females, 121 males) with 90 cases under the age of 16 years. Two hundred eighty-eight patients (97.9%) and six (2.1%) patients had early(within 6 h after ingestion) and delayed(6 h to 20 d) toxicity symptoms, respectively. The onset of symptoms was within two hours for 101 patients (34.3%). The most common first-noticed symptoms were in the gastrointestinal system. The patients were discharged within one to ten days. Three patients suffering from poisoning caused by wild mushrooms died from fulminant hepatic failure. Barbee GA et al.[14] from Texas,USA, noted that of 742 acute and intentional mushroom exposures during 2005 to 2006,59 (7.9%) (male to female ratio 3.3:1) were admitted to the hospital, with 17 (28.8% of admissions) requiring admission to a critical care unit, four cases requiring inpatient psychiatric admission. Psilocybin being the most

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common agent (n=10, 91%).The most common symptoms in admitted patients were vomiting (n=34, 57.6%), nausea (n=19, 32.2%), altered mental status (n=17, 28.8%), abdominalpain (n=13, 22%) and diarrhoea (n=10, 16.9%).They concluded that major toxic reactions were uncommon, no deaths were reported and hence serious poisoning from mushroom ingestion is rare in Texas. Schenk-Jaeger KM et al.[15] from Switzerlandanalyzed5638 cases reported to the Swiss Toxicological Information Centre between January 1995 and December 2009 and found that severe symptoms have not only been observed after ingestion of non-amatoxin-containing toxic mushrooms, i.e. ***Boletus sp.*** and ***Cortinarius sp.***, but also after meals of edible species. The mortality of confirmed amatoxin poisonings was high (5/32) compared to other reports. Many of the centers in the West have included Liver Transplant as a treatment in fulminant liver failure following mushroom poisoning.[21] In those centers where facilities for liver transplant is not feasible, mortality is very high, especially when fulminant hepatic failure sets in.[2,3,18-20] As there is no definite antidote, preventing acute hepatic injury is the best option available. We know from various observations that diarrhea and vomiting are the initial symptoms which lead to pre-renal failure and farther reduce the excretion of the toxins. Moreover, studies in dogs have shown that the toxin is excreted in the bile.[22] Much of the toxin excreted in this way is reabsorbed into the liver with the bile. Fauser and Faulstich in 1973 showed that interruption of the cycling of the toxin by bile duct cannulation can reduce the toxic effects of α-amantin in dogs.[23] So we tried two simple clinical management of keeping the patient nil orally for 48 to 72 with an indwelling nasogastric tube which was frequently aspirated and early hydration of patients with intravenous crystalloids so that the pre-renal failure could be prevented. This simple modification in our treatment strategy has shown significant decrease in mortality (OR 0.2063) and morbidity including acute liver failure (OR 0.356) and acute kidney injury (OR 0.285).

CONCLUSION

Early hydration therapy and nasogastric aspiration of bile significantly reduces the mortality and morbidity in patients coming with signs and symptoms of mushroom poisoning.

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Table 2 : Demographic profile of cases admitted with history of mushroom poisoning.

Parameters		No. of cases (n = 94)	Percentage	No. of cases expired (n = 13)	Percentage
Age (years)					
	< 20	19	20.2%	2	15.4%
	20-29	26	27.7%	0	-
	30-39	21	22.3%	5	38.5%
	40-49	19	20.2%	6	46.1%
	50-59	7	7.4%	0	-
	>60	2	2.1%	0	-
Sex					
	Male	37	39.4%	8	21.6%
	Female	57	60.6%	5	8.8%
Outbreak					
	April-May 2014	69	73.4%	7	10.1%
	August 2014	5	5.3%	0	-
	April 2015	20	21.3%	6	30%
Clinical presentation					
	Loose stool	89	94.7%	13	100%
	Vomiting	76	80.9%	11	84.6%
	Hypotension	54	57.4%	13	100%
	Pain Abdomen	68	72.3%	7	53.8%
	Dryness of mouth	48	51.1%	13	100%
	Icterus	47	50%	8	61.5%
	Altered behavior	18	19.1%	5	38.5%
	Seizure	23	24.5%	7	53.8%
	Bleeding diathesis	3	3.2%	3	23.1%
	Uremia	9	9.6%	4	30.8%

Table 2 : Laboratory findings of our study population with history of Mushroom poisoning.

Laboratory finding(Units)	**Mean values for study population** (n = 94)	**Mean values for fatal cases** (n = 13)
AST (IU/L)	528 ± 57	2324 ±189
ALT (IU/L)	872 ± 93	3164 ± 158
Serum creatinine (mg/dl)	1.7 ± 0.5	2.4 ± 0.4
Prothrombin Time (secs)	9.1 ±2	27.9 ± 5

The Laboratory parameters of fatal cases show a higher level of liver enzymes (AST and ALT) , serum creatinine and Prothrombin time. (Table 2)

Table3: Comparison of mortality and morbidity amongst mushroom poisoning patients treated with early hydration therapy and those with only symptomatic treatment

Clinical outcome	**Patients with early Hydration (Case) n = 94**		**Symptomatic treatment (Control) n = 48[2]**		**Odds Ratio**	**p-Value**
	Number	Percentage (%)	Number	Percentage (%)		
Mortality	13	13.83%	21	43.75	0.2063	<0.001
Hypovolemic Shock	2	2.13%	11	22.9%	0.073	<0.001
Acute Liver Failure	37	39.36%	31	64.58%	0.356	0.0044
Acute Kidney Injury	9	9.57%	13	27%	0.285	0.0064
Bleeding manifestations	3	3.19%	7	14.58%	0.193	0.0121

Table 4: Comparative review of mushroom poisoning cases reported worldwide and from India

Year of Research Publication	**Institute**	**Geographic Region**	**Authors**	**Number of fatal cases Reported**
Oct 1994	PGIMER, Chandigarh	North India	Singh S et al.[16]	5 (0)
2003	Military Hospital, Dehradun	Uttaranchal	Garg MS et al.[17]	4 (2)
Jan 2007	Tansen Mission Hospital	Nepal, 2005	Joshi A et al.[18]	34 (12)
2008	Saidu Hospital Swat	Abbottabad, Pakistan, 2006	Jan MA et al.[19]	18 (13)
June 2009	Womack Army Medical Center	Texas, USA, 2005-2006	Barbee GA et al.[14]	742 (0)
May 2010	Cumhuriyet University Hospital	Sivas, Turkey 2000 to 2007	Eren SH et al.[13]	294 (3)
June 2012	University of Zurich	Switzerland 1995-2009	Schenk-Jaeger KM et al.[15]	5638 reviewed 32(5) amatoxin
July 2013	AMCH, Dibrugarh, Assam	Dibrugarh, Assam, 2009	Dutta A et al.[2]	48 (21)
Sep 2013	Joint director of health Services,Lakhimpur	Lakhimpur district, Assam, 2011,2012,2013	Sharma J et al.[3]	68 (10)
Dec 2014	PGIMER, Chandigarh	Himachal Pradesh, Sep 2011	Verma N et al.[20]	4 (3)
Present Study	AMCH, Dibrugarh, Assam	April-May 2014, August 2014, April 2015	Dutta A et al.	94 (13)