

The Effects of N-acetylcysteine in Patients with *Amanita phalloides* Intoxication

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Abstract

Objectives: Mushroom intoxication with *Amanita phalloides* has a high incidence throughout the world. Treatment for this intoxication is similar in different centers, but N-acetylcysteine is rarely used. In this study, we aimed to investigate the effects of N-acetylcysteine treatment in patients with *Amanita phalloides* intoxication.

Methods: A total of 40 patients with *Amanita phalloides* intoxication were included in this retrospective study. The study group consisted of 24 patients who were administered N-acetylcysteine in addition to the standard regimen; the control group consisted of 16 patients who were treated only with the standard treatment. Treatment results and biochemical measurements of groups were compared.

Results: According to the biochemical measurements, it was found that patients in the control group were affected more seriously by *Amanita phalloides* than those in the study group. The mortality rate was lower in the study group (4.4% vs. 18.7% in the control group).

Conclusions: *Amanita phalloides* intoxication can be successfully treated with N-acetylcysteine in addition to the standard regimen. Significantly, the simplicity of administration, good tolerance, and an affordable cost make N-acetylcysteine a viable option for the treatment of *Amanita phalloides* intoxication. The low mortality rate presented in the study group may be ascribed to N-acetylcysteine administration.

Keywords: *Amanita phalloides*; Intoxication; N-acetylcysteine

Introduction

Mushroom intoxication is the most common vegetal intoxications in Turkey and in other parts of the world [1,2]. It may result in several disorders, ranging from mild gastroenteritis to severe fulminant hepatic failure. The main cause of mortality is amatoxin, *Amanita phalloides* (*A. phalloides*) toxin, which leads to very high mortality rates up to >20% in adults and >50% in children [3]. Amatoxin noncompetitively inhibits RNA polymerase II or B, which is dependent on DNA. Bromelain, cysteine proteinase, cathepsin, cathepsin L, and papain are released [4]. Inhibition of mRNA synthesis in hepatocytes causes a decrease in coagulation factor and immunoglobulin production. In addition, another toxin, phallotoxin, tends to adhere to microfilament structures and causes cholestasis by stabilizing F actin filaments. Although the main target tissue of *A. phalloides* is the liver, kidney cells may also be affected. Expectedly, intoxication frequency exhibits seasonal variation, with a significant increase during fall, concurrent with the rains.

N-acetylcysteine (NAC) has anti-inflammatory, antioxidant, inotropic, and vasodilating effects that improve microcirculatory blood flow and oxygen delivery to vital organs [5]. It also supplies sulphhydryl groups to act as a substrate for detoxifying reactive toxic intermediates [6]. NAC may benefit patients with non-acetaminophen-induced acute liver failure by improving systemic hemodynamics via tissue oxygen delivery or other favorable effects on the acutely injured liver. Benefits are seen when NAC is used in the early stages of liver failure [7]. Studies on the effects of NAC on *Amanita phalloides* intoxication are very rare. Furthermore, in some previous research, NAC was administered with the standard regimen, which includes silibinin and other treatments such as plasmapheresis, so it is difficult to show the clear effect of NAC on *A. phalloides* intoxication in these studies [8-10]. In the present

research, we aimed to investigate the benefits of N-acetylcysteine treatment in addition to the standard treatment in patients with *A. phalloides* intoxication.

Material and Methods

In this study, data from 40 patients with *A. phalloides* intoxication who were treated at the Internal Medicine Clinic of our institute from 2001 to 2006 were studied retrospectively. The institutional review board of our hospital approved the study. Mushroom intoxication patients with any comorbidity and/or patients who were admitted to the hospital more than 24 hours after ingestion were excluded.

Patients were divided into two groups. The study group consisted of 24 patients who were administered N-acetylcysteine in addition to the standard regimen, while the control group consisted of 16 patients who were treated only with the standard treatment. According to the standard treatment, nasogastric tubes and gastric enemas were applied to patients who presented in the first 24 hours. Additionally, hemoperfusion was performed, and intravenous penicillin G (1 million units/kg/day) infusion, activated charcoal (5 g/day), and lactulose (4 g/day) were administered in three divided

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doses. Furthermore, as a conservative and supportive therapy, 10% dextrose 100 cc/h+hepatamine 500 cc/day and fresh frozen plasma (FFP) were administered intravenously after evaluating coagulation tests and ensuring > 70% prothrombin activity. The total dose of NAC administered to the patients in the study group was 12 g/day. This was administered intravenously in four divided doses.

AST, ALT, LDH, and INR levels of patients at 24 hours, 48 hours, 72 hours, 1 week, and 2 weeks after mushroom ingestion were reported. The mean values of groups were compared. The MedCalc 12.7 software program (MedCalc, Turkey) was used for the statistical analysis, and data were reported as the mean ± standard deviation (SD). The Chi square and Kolmogorov-Smirnov tests were used to compare the categorical measurements (gender distribution and mortality rate) between the groups, and to show the normal distribution of the quantitative measurements, respectively. The independent groups t-test or Mann Whitney U test was used for the comparison of the AST, ALT, LDH, and INR levels between the two groups.

Results

The mean ages of the study and control groups were 32.0 ± 15.4 and 34.0 ± 16.5, respectively. The female to male ratio was 14:26 (35% female vs. 65% male). There were eight (33.3%) and six (37.5%) women in the study and control groups, respectively. There were no statistically significant differences between the groups according to age and gender distribution (p=0.70, p=0.94, respectively; Table 1).

Groups were compared according to the duration from ingestion to admission (p=0.21; Table 1). Patients in the control group were affected more seriously by *A. phalloides* than those in the study group. Although there was no statistically significant difference between the groups according to the biochemical measurements (AST, ALT, LDH, INR) at 24 hours, there was a statistically significant difference at 48 hours, 72 hours, 1 week, and 2 weeks according to most of the measurements (Table 2). Biochemical measurements for patients in the study group were lower than those for the control group. Moreover, the frequency of death due to fulminant hepatic failure was lower in the study group (4.4% in the study group vs. 18.7% in the control group; Table 1).

Discussion

In this study, we showed a successful method of treating *Amanita phalloides* intoxication with N-acetylcysteine in addition to the standard regimen. The mortality rate was lower than 5% in the study group, while it was 18% in the control group.

Mushroom intoxication with *A. phalloides* is common in Turkey. This is associated with fulminant hepatic failure and a high mortality rate. The mortality rate from *A. phalloides* intoxication is > 20% in adults and > 50% in children, even when treated aggressively [4].

A. phalloides intoxication is treated similarly in different centers. The treatment methods include gastric enema, active charcoal application, forced diuresis, and extracorporeal detoxification. The

	Study group (N=24)	Control group (N=16)	p
Age	32 ± 15.4	34 ± 16.5	0.70
Female N (%)	8 (33.3%)	6 (37.5%)	0.94
Time for ingestion to admission (hours)	8.3 ± 4.2	10.0 ± 3.7	0.21
Mortality rate N (%)	1 (4.4%)	3 (18.7%)	0.35

Table 1: Characteristics of the groups.

	Study group (N=24)	Control group (N=16)	p
24 hours			
AST	236 ± 45	242 ± 34	0.61
ALT	186 ± 36	197 ± 28	0.30
LDH	432 ± 144	416 ± 111	0.71
INR	1.03 ± 0.16	1.04 ± 0.17	0.92
48 hours			
AST	1831 ± 200	2086 ± 347	0.005
ALT	1714 ± 253	1918 ± 327	0.03
LDH	2237 ± 364	2180 ± 431	0.65
INR	1.94 ± 0.4	2.09 ± 0.4	0.26
72 hours			
AST	3324 ± 541	3878 ± 757	0.01
ALT	2253 ± 306	2706 ± 912	0.03
LDH	2785 ± 301	3532 ± 567	<0.001
INR	2.15 ± 0.52	2.62 ± 0.65	0.01
1 st week			
AST	550 ± 97	1139 ± 404	<0.001
ALT	293 ± 94	804 ± 334	<0.001
LDH	519 ± 64	1207 ± 283	<0.001
INR	1.53 ± 0.42	1.42 ± 0.25	0.40
2 nd week			
AST	32.3 ± 7.8	41.2 ± 12.8	0.01
ALT	37 ± 10	43 ± 5	0.05
LDH	295 ± 54	346 ± 112	0.07
INR	1.06 ± 0.16	1.1 ± 0.17	0.54

Table 2: Comparison of AST, ALT, LDH and INR of the groups.

most efficient procedures are hemoperfusion and plasmapheresis. High-dose penicillin and silibinin are used to block toxins from gaining access to hepatocytes [4,11-15]. Silibinin is also used for damaged liver cell regeneration. It should be noted that we were unable to use silibinin in our patients, since it is not locally available in our country.

In previous studies, Montanini et al. reported that 11 patients with *A. phalloides* intoxication were treated successfully with NAC in addition to the standard treatment [16]. Similarly, Boyer et al. reported the successful treatment of a pregnant woman (twelve weeks) with NAC in addition to the standard protocol [17]. Both of these reports are in accordance with our study, but their sample sizes were small. Although the results of some of these studies are similar to ours, there were also some differences in the treatment methods used. For example, Bergis et al. treated *A. phalloides* intoxication with NAC in addition to the standard regimen with silibinin and plasmapheresis [8]. Their treatment was successful but the extent of the effect of NAC was not clear due because silibinin and plasmapheresis were also used. In another study, Grabhorn et al. reported successful outcomes for the treatment of *A. phalloides* poisoning in children with active charcoal, silibinin, and NAC [9]. Lastly, Ahishali et al. reported low mortality rate in patients with mushroom intoxication who were administered NAC, silibinin, and hemofiltration in addition to the standard regimen [10]. In these works, it cannot be determined whether the successful outcomes resulted from NAC, silibinin, or hemofiltration use. Moreover, the sample sizes in most of these studies were smaller than that in our study.

The low mortality rate presented in our study group may be ascribed to NAC administration. Roberts et al. reported that the mortality rate from *A. phalloides* was high despite treatment according to the standard, including silibinin [18]. Consequently, the mortality rate might be lower if NAC were administered to patients.

N-acetylcysteine is used for paracetamol intoxication to decrease the extent of hepatocellular damage. It enhances glutathione stores, acts as a glutathione substrate, and promotes conjugation by the nontoxic sulfonic pathway [19].

In this study, NAC was administered within 24 hours after the ingestion of mushrooms. When we analyzed the biochemical measurements, we observed that the levels of AST, ALT, LDH, and INR of patients in the study group were lower than those in the control group at different times. Furthermore, the patients in the study group recovered more quickly from intoxication. Additionally, frequency of death from intoxication due to the hepatic failure was lower than among patients in the control group.

As a limitation of this study, the blood and urinary alpha amanitin levels of patients were not measured, since this was not possible in our institute in the years the patients were treated. However, the clinical presentation and hepatotoxicity of the patients were consistent with *A. phalloides* intoxication.

In conclusion, the mortality rate (<5%) was lower in our study compared to previously reported data [4,11,18]. *Amanita phalloides* intoxication can be successfully treated with N-acetylcysteine in addition to the standard regimen. Significantly, the simplicity of administration, good tolerance, and affordable cost make NAC a viable option for the treatment of *A. phalloides* intoxication.

Finally, we suggest that the media should have an important role in teaching the public about the danger of mushroom intoxication. Health institutions should be more active in enlightening the public on this critical subject. Education regarding mushroom poisoning should probably begin during early childhood. New, more effective treatment options should be developed for such dangerous intoxications.

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