

Comparing the Therapeutic Effectiveness of N-acetylcysteine with the Combination of N-acetyl Cysteine and Cimetidine in Acute Acetaminophen Toxicity: A Double-Blinded Clinical TrialMohsen Ebrahimi¹, Seyed Reza Mousavi², Alireza Ghassemi Toussi³, Hamidreza Reihani¹, Farhad Bagherian⁴¹Emergency Medicine Department, Imam Reza Hospital, Mashhad University of Medical Sciences, Mashhad, Iran² Medical Toxicology Research Center, Department of Clinical Toxicology, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran³Addiction Research Center, Imam Reza Hospital, Mashhad University of Medical Sciences, Mashhad, Iran⁴Emergency Medicine Department, Peymanieh Hospital, Jahrom University of Medical Sciences, Jahrom, Iran**Type of article:** Original**Abstract**

Background: N-acetylcysteine (NAC) has been used as a classic treatment for hepatotoxicity induced by N-acetyl-p-benzoquinone imine (NAPQI) as a metabolite of acetaminophen. However, cimetidine theoretically can reduce the production of toxic metabolites through the inhibition of cytochrome p450, and it recently was proposed as a complementary treatment for acetaminophen toxicity.

Objective: The aim of this study was to compare the effects of treating acute acetaminophen toxicity with NAC alone and with a combination of NAC and cimetidine.

Methods: From October 2013 to March 2014, 105 patients suspected of acetaminophen toxicity who had paraclinical confirmation of toxicity requiring medical treatment (based on the risk assessment nomogram of acetaminophen serum level) were enrolled in this double-blind, randomized, controlled trial at Imam Reza Hospital in Mashhad, Iran. The patients were divided into two groups, i.e., 1) patients who were treated with NAC alone (group A) and 2) patients who were treated with a combination of NAC and cimetidine (group B). The primary outcomes were 1) the serum level of acetaminophen and 2) the serum level of aminotransferases at the time of admission and 4, 12, 24, and 48 hours after admission. Exclusion criteria included multiple toxicities, concurrent diseases that could affect liver enzymes, the use of other drugs, and dissatisfaction with the project. For measuring quantitative data, SPSS version 16 was used for t-test analysis and for analyzing the qualitative data with chi-squared analysis.

Results: Sixty patients (32 females and 28 males) with a mean age of 25.2 ± 7.3 years were classified in two groups of 30. There was no difference between the groups in terms of their admission information. The average levels of acetaminophen in both groups at admission, 12, 24, and 48 hours after hospitalization were not significantly different from each other. Twelve hours after hospitalization, the aspartate aminotransferase (AST) level in the group treated with NAC was significantly higher than in the group treated with the combination of NAC and cimetidine ($\text{IU/L} 30.1 \pm 110.0$ versus $\text{IU/L} 26.38 \pm 94.93$, $p = 0.044$). At the other times that the level of liver enzymes was assessed, the serum levels of urea and creatinine were not significantly different in the two groups ($p > 0.05$).

Conclusion: The intravenous administration of 300 mg of cimetidine every six hours with NAC did not improve the level of hepatoprotective action significantly compared with the NAC treatment protocol alone.

Trial registration: The trial was registered at the Iranian Clinical Trial Registry (IRCT.ir) with the IRCT identification number IRCT2013102915204N1.

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Keywords: acetaminophen, acetylcysteine, cimetidine, toxicity

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1. Introduction

Acute acetaminophen toxicity is very prevalent because of the wide range of therapeutic applications of this drug and its availability (1). Overdoses of acetaminophen are the most common causes of acute liver failure in America (1-7). Nausea, vomiting, diarrhea, abdominal pain, and shock are the adverse effects of this drug, and they can occur within 4-12 hours after the drug is taken. Then, after 24-48 hours, increases in the liver aminotransferases appear, which is indicative of liver damage (7). Very high mortality of this toxicity (especially liver failure), lack of feasibility of the treatment, and the need to reduce the side effects of this type of toxicity have led specialists to increasingly use N-acetylcysteine (NAC) as the classical treatment for this toxicity. Acetaminophen is converted mainly to neutral and harmless compounds by the Type II reaction (3-4). But a small part of it undergoes the Type I reaction (cytochrome p450), which converts the acetaminophen to a certain toxic metabolite, called N-acetyl-p-benzoquinone imine (NAPQI) leading to central damage of the hepatic lobules (8). Theoretically, cimetidine has the ability to reduce the production of toxic metabolites through the inhibition of cytochrome, and it has been proposed recently as a complementary treatment (9, 10). Given that cimetidine is an available drug and its side effects are known and occur only at very high doses, its use in combination with NAC may be effective in treating acute acetaminophen toxicity (11). The purpose of this study was to compare the effects of treating acute acetaminophen toxicity using a combination of cimetidine and NAC and treating this toxicity with NAC alone.

2. Material and Methods

2.1. Trial Design

This study was a single-center, prospective, double-blind, randomized controlled trial that was approved by the Research Council of Mashhad University of Medical Sciences. Patients suspected of having acetaminophen toxicity who had paraclinical confirmation of toxicity requiring medical treatment (based on the risk assessment nomogram of acetaminophen serum level) were admitted to the Toxicology Emergency Ward at Imam Reza Hospital in Mashhad, Iran, from October 2013 to March 2014, were enrolled in the study. The patients were divided into two groups, i.e., 1) patients who were treated with NAC alone (group A) and 2) patients who were treated with a combination of NAC and cimetidine (group B). The patients were allocated randomly to the two groups. The primary outcome was acetaminophen serum level, and 2) aminotransferases serum level, at the time of admission and 4, 12, 24 and 48 hours after admission.

2.2. Participants and sampling

All patients with acute acetaminophen poisoning within 12 hours after taking the drug and who were at least 18 years old were enrolled in the study. Patients with multiple poisonings, patients with comorbidity (e.g., heart failure, congenital liver problems, and hepatitis) and patients with regularly consume drugs or who recently (less than one week) consumed drugs were excluded. According to the sample size formula, $n = \sigma^2(Z_\alpha + Z_\beta)^2 / d^2$, assuming an alpha error of 5% and a study power of 80%, including a 20% loss, the sample size was determined to be 30 subjects for each group.

2.3. Interventions

After determining the level of serum acetaminophen, at least four hours after taking and confirming acetaminophen toxicity, NAC (Darou Pakhsh Company of Iran) was administered to the first group of patients according to the following protocol, i.e., an initial dose of 150 mg/kg for 20 minutes, the next dose of 50 mg/kg within 4 hours, and the third dose of 100 mg/kg within 16 hours. The second group received the same regimen of injections of NAC as the first group (12), but they also received 300 mg of cimetidine every six hours, in accordance with Burkhardt et al.'s study (12).

2.4. Outcomes

Before the interventions, the patients' basic information was recorded, including age; gender; symptoms of toxicity, consisting of abdominal pain, abdominal discomfort, loss of appetite, jaundice, itching; and the elapsed time from poisoning to the first visit by the emergency medicine resident who was unaware of the two groups of patients. For standardization, all of the patients' samples were taken and investigated by one of the laboratory personnel. Moreover, the common protocol for monitoring liver damage was performed in all patients. Serum levels of acetaminophen (AST) and aminotransferases (ALT) were determined at the time of admission and 4, 12, 24, and 48 hours after admission. Also, urea and creatinine in patients were gauged in terms of the incidence of acute renal failure at admission and 24 hours after admission. In line with standardization, all of the patients' samples were taken and investigated by one of the laboratory personnel.

2.5. Randomization

Using a table of random numbers, the patients were divided into two groups, i.e., one group that was treated with injected NAC and a second group that was treated with injected NAC and intravenous cimetidine.

2.6. Blinding

In this double-blinded study, all patients suspected of having acetaminophen toxicity were included in a separate list in the toxicology ward by the head nurse of the unit who was blind to the study protocol. We used numbered envelopes that contained one of the two treatment protocols to classify the patients into one of the two groups. The treatment plan of each group was prepared by the nurse and delivered to the investigator. The patient was not aware to the type of solution that was used.

2.7. Statistical methods

Required information about this project was extracted based on various checklists. A computer was used to collect the data and enter them into the software's database. SPSS 16 software was used to conduct statistical analyses of the data. The t-test analysis was used to evaluate the quantitative data, and the chi-squared test was used to analyze the qualitative data. The confidence level of 0.95 was considered for the project. In order to compare pharmacotherapy to reduce the levels of aminotransferases in the liver in the two groups, independent-2-sample-t test analysis was used, and, if necessary, its non-parametric equivalent was used.

2.8. Research ethics

This study was approved by the Medical Ethics Committee of Mashhad University of Medical Sciences. All patients were informed about the processes involved in the project before they agreed to participate, and their data were used to implement the project. Privacy and respecting the patients' dignity were carefully adhered to during the implementation of the project. All of the patients' data were coded and inserted into statistical analysis applications, and the results were published.

3. Results

3.1. Baseline characteristics

During the six-month period of study, 105 patients suspected of having acetaminophen toxicity who were hospitalized in the Emergency Department of the Medical Toxicology Center of Imam Reza Hospital were considered for the study. Forty-five of the patients met one or more of the exclusion criteria, so the study was conducted with the remaining 60 patients who were divided into two groups of 30 patients each. The results of 60 patients were analyzed statistically. The 45 patients who were excluded from the study consisted of 10 patients who did not meet the inclusion criteria, three patients who had multiple toxicities, seven patients who had concurrent diseases, 13 patients who were using other drugs, and 12 patients who chose not to participate (Figure 1).

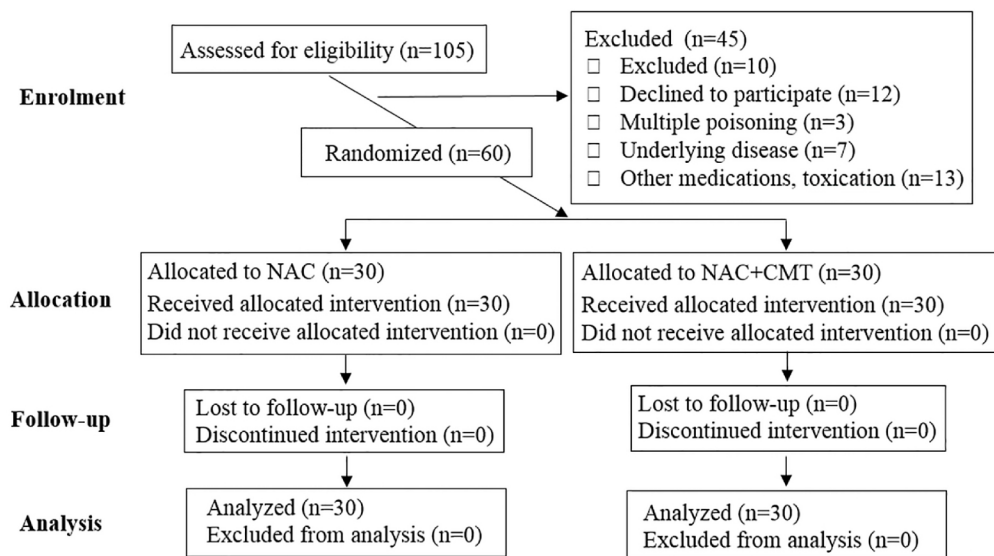


Figure 1. Follow-up diagram of patients suspected of having acetaminophen poisoning who were admitted to the Emergency Department of Toxicology (according to consort statement)

In this study, 60 patients (32 females and 28 males) with a mean age of 25.2 ± 7.3 years were classified in two groups of 30. The two groups treated with NAC alone and the combination of NAC and cimetidine were not significantly different in terms of the main variables of age, gender, serum levels of acetaminophen and severity of poisoning symptoms, the time elapsed after poisoning to the first visit, and the liver enzyme-based tests, i.e., urea and creatinine (Table 1). None of the members of the two groups had undergone therapeutic intervention before hospitalization. The most common manifestation of toxicity in patients was loss of appetite, which was observed in 40 patients (67%). Pruritus (itching) was the least reported disorder in the survey, with only three patients reporting this symptom. Nine patients had abdominal pains, and 12 patients complained about a feeling of abdominal discomfort.

Table 1. Variables related to the characteristics of admission of participants in the two groups of N acetylcysteine (NAC) and N- acetylcysteine with cimetidine (NAC + CMT)

Variables	NAC group (n = 30)	NAC+CMT group (n = 30)	p-value
Age, year (Mean \pm SD)	35.8 ± 15.2	39.7 ± 18.0	0.27
Abdominal pain, n (%)	4 (13.3)	5 (16.7)	0.999
Abdominal discomfort, n (%)	6 (20.0)	6 (20.0)	0.999
Loss of appetite, n (%)	20 (66.7)	20 (66.7)	0.999
Jaundice, n (%)	0 (0.0)	0 (0.0)	0.999
Itching, n (%)	2 (6.7)	1 (3.3)	0.999
Elapsed time from poisoning to the first visit, hour (Mean \pm SD)	8.9 ± 5.4	9.34 ± 4.80	0.301
Acetaminophen serum level, $\mu\text{g/mL}$ (Mean \pm SD)	94.5 ± 34.2	92.1 ± 40.38	0.805
alanine aminotransferase (ALT) serum level, mg/dL (Mean \pm SD)	131.4 ± 41.9	125.5 ± 41.18	0.584
Aspartate aminotransferase (AST) serum level, mg/dL (Mean \pm SD)	132.0 ± 36.2	121.2 ± 32.2	0.229
Urea serum level, mg/dL (Mean \pm SD)	30.4 ± 7.3	29.2 ± 6.4	0.513
Creatinine serum level, mg/dL (Mean \pm SD)	0.65 ± 0.29	0.74 ± 0.17	0.158

3.2. Serum acetaminophen level

The t-test showed that the mean serum levels of acetaminophen in the two groups at 12, 24, and 48 hours after hospitalization were not significantly different. In both groups, the serum level of acetaminophen 48 hours after admission was zero ($p > 0.999$). Thus, the toxicity of the liver was treated successfully in all patients (Table 2).

Table 2. Comparison of serum levels (Mean \pm SD) of acetaminophen, aspartate aminotransferase (AST), alanine aminotransferase (ALT), urea, and creatinine between the two groups treated with N-acetylcysteine (NAC) and N-acetylcysteine with cimetidine (NAC + CMT)

Elapsed time from poisoning	Groups	Serum Acetaminophen ¹	Serum AST ²	Serum ALT ²	Serum Urea ²	Serum Creatinine ²
12 hours	NAC + CMT	24.9 ± 13.8	94.9 ± 26.3	89.4 ± 35.2		
	NAC	26.9 ± 12.6	110.0 ± 30.1	102.3 ± 37.8		
	P-value	0.554	0.044	0.178		
24 hours	NAC + CMT	6.9 ± 4.5	73.6 ± 18.5	73.3 ± 22.6	25.2 ± 4.5	0.6 ± 0.1
	NAC	7.2 ± 5.8	81.2 ± 22.4	75.9 ± 20.2	27.0 ± 5.6	0.6 ± 0.2
	P-value	0.468	0.158	0.645	0.197	0.562
48 hours	NAC + CMT	0.0 ± 0.0	57.8 ± 14.3	56.2 ± 13.0		
	NAC	0.0 ± 0.0	55.1 ± 11.8	51.3 ± 12.3		
	P-value	0.999	0.430	0.147		

1: measured in $\mu\text{g/mL}$; 2: measured in mg/dL

3.3. Serum aminotransferases levels

Based on the t-test statistical test, the AST levels at the time of hospitalization were not significantly different in the two groups ($p > 0.999$). Over 12 hours of hospitalization of the group treated with N- NAC, the AST level was significantly higher than it was in the group treated with the combination of NAC and cimetidine (110.0 ± 30.1 IU/L versus 94.93 ± 26.38 IU/L; $p = 0.044$). At 24 and 48 hours after admission, no significant difference was observed between the level of AST in the two groups ($p > 0.05$) (Table 2). Based on the t-test statistical analysis, the ALT level was not significantly different at the time of hospitalization ($p > 0.999$). Also, the average ALT levels for the

two groups at 12, 24, and 48 hours after admission were not significantly different for the two groups ($p > 0.05$) (Table 2).

3.4. Levels of serum urea and creatinine

Based on the t-test statistical analysis, at the time of hospitalization and 12 hours after admission, the serum levels of urea and creatinine were not significantly different for the two groups ($p > 0.05$) (Table 2).

3.5. Side effects

No side effects were observed in any of the patients. Moreover, none of the patients died. Further, there was no statistically significant difference between the two groups in terms of the number days the participants were hospitalized (1.2 ± 2.1 days versus 1.4 ± 2.3 days, $p = 0.523$).

4. Discussion

The results of this study showed that the administration of intravenous cimetidine in combination with NAC after 12 hours acetaminophen toxicity did not result in significantly improved liver function compared with the protocol of NAC treatment alone. When acetaminophen is ingested, more than 90% is metabolized by sulphitation and glucuronidation and 5% is metabolized by cytochrome P450 in an oxidation system (13). N-acetyl-p-benzoquinone imine (NAPQI) is the only acetaminophen metabolite produced through the oxidation system, and it is routinely neutralized by glutathione; however, in large quantities of NAPQI and lacking neutralization by glutathione, it can cause damage to the hepatocytes and death (11, 13, 14). NAC acts as a precursor or a substitute for glutathione, and the cimetidine mechanism inhibits the formation of cytochrome P450. In this way, it can prevent the formation of the oxidative metabolites of acetaminophen, therefore we can expect theoretically a longer liver protection until complete detoxification occurs (12, 13, 15). However, this theory was not well confirmed in this study. The first and the most sensitive tests in the early hours of toxicity to assess liver involvement include measurements of ALT, AST, bilirubin, prothrombin, and creatinine (11).

In this study, we examined these variables followed by acetaminophen toxicity in both treatment groups, and no significant changes were observed in prothrombin times and creatinine levels between the two treatment protocols in any of the studied periods. In the liver involvement, it was expected that transaminases would reach their maximum value within 16 to 24 hours, and hypertransaminasemia is the most important laboratory parameter for liver involvement (12). In this study, in both groups, the level of transaminases decreased over time, as did the level of acetaminophen, denoting the effect of both therapeutic compounds. The level of ALT liver enzyme was not significantly different in the two groups during the performance of the four tests over a period of 48 hours. But the level of AST liver enzyme at 12 hours after admission was significantly less in the group treated with the combination of NAC and cimetidine, indicating that the treatment was better for protecting hepatocytes than NAC alone. If this observation is correct, it seems that the other causes for this significant difference are the mechanism of cimetidine action on reducing hepatic blood flow and reducing the absorption of acetaminophen (16). But it should be considered that to evaluate the therapeutic effects changes of ALT have greater sensitivity and specificity associated with changes in hepatocytes, so assessing the changes in the ALT levels is more valuable than assessing changes in AST (8). In this study, like other human studies, significant changes were not found in the ALT level of the group treated with cimetidine. In a study by Burkhart et al. (12), no significant difference was observed between AST and ALT levels in the two groups of patients. In Burkhart et al.'s study (12), it was mentioned that the probable causes for the lack of enhanced effectiveness with the combination of NAC and cimetidine were various factors, such as long intervals (an average of 14 hours), time of the overdose of acetaminophen, and the time the treatment began. In another study by Chen et al. (10), it was found that cimetidine does not lead to changes in the pharmacokinetics of acetaminophen. To date, in four other human studies, the effects of cimetidine on the metabolism of acetaminophen have been investigated. In another study, it was proven that acetaminophen's half-life and elimination did not change when cimetidine was used (17). In another study, it was indicated that the consumption of 800 mg per hour of cimetidine for an hour before taking 20 mg/kg of acetaminophen and a dose of 400 mg/kg every four hours for 12 hours after the consumption of acetaminophen did not lead to any change in the level of secretion of its oxidative metabolites (18). In another study, it also was found that the consumption of cimetidine two days before taking 1.5 grams of acetaminophen did not cause any oxidative metabolites of acetaminophen (19). However, in the majority of the findings in the animal studies, in contrast to human studies, cimetidine clearly has been proven effective in protecting the liver after overdoses of acetaminophen (20). In an animal study, it was demonstrated that using a relatively low dose of cimetidine, i.e., 8.5 mg/kg, before the injection

of as much acetaminophen as 750 mg/kg significantly reduced the elevated level of ALT (20). A notable point in this animal study was the early injection of cimetidine. It seems that, using the results of this animal research, our hypothesis should state that cimetidine is more effective when is administered in the early hours before the inclusion of acetaminophen in the metabolization cycle. In fact, the effect of taking more cimetidine will be observed in the early hours, because acetaminophen is converted to its metabolites and absorbed up to that time (10, 12). However, it should be noted that the referral time in most people with acetaminophen poisonings will not be immediate, and they will wait until the onset of symptoms, which may usually take about 8 hours (12). In our study, this time was averaged more than 12 hours. In this case, it seems that belated prescription of cimetidine is one of the reasons for the lack of difference between the two modalities that were used to treat acetaminophen toxicity. However, it should be noted that, in animal studies, high doses of 100 mg or more per kg of cimetidine are used. In another study conducted on rats, using cimetidine with the dose of 120 mg per kg at the time of 4-10 hours after acetaminophen overdose clearly improved the rate of survival in rats. But using NAC (at a dose of 1 g per kg), the improvement in survival was not significant (19).

The results of this study highlighted the role of the dose required to enhance the effectiveness of cimetidine. This was in agreement with the results of another study in which the administration of the combination of NAC and cimetidine produced significantly improved survival and reduced levels of transaminases than using NAC alone (21). Burkhart et al. conducted a study in which it was pointed out that that survival was increased by increasing the cimetidine dosage or by reducing the frequency of administration of the cimetidine. Moreover, prescribing practices in animal models are completely different from those with human subjects. In animal studies, administering cimetidine is mostly conducted intraperitoneally, whereas, in human studies, including ours, use intravenous administration, and this could be one reason for the difference in the effect. However, since taking cimetidine has not produced any no complications and side effects rarely occur, using it in combination with NAC seems to be safe due to its ability to better reduce the ALT level 12 hours after taking the first therapeutic dose. This finding corresponds with the findings of Chen et al.'s (10) research. However, it should be understood that this drug can be associated with complications, such as disorientation, hallucinations, psychosis and agitation, thrombocytopenia, and leukopenia, which occur mainly in elderly patients in less than 5% of the cases. However, its complications rarely can be managed easily (22-24). To determine other things that can cause the lack of clear influence of cimetidine in human studies as opposed to animal studies, the mechanism of cytochrome P450 must be investigated (8, 13). It seems that cimetidine in rodents has higher inhibition for cytochrome P450 and this difference in different animal species also had made a difference in the incidence of acetaminophen-induced cytotoxicity (12). In a study conducted by Laine et al. (8), it was found that CYP3A4 and, subsequently, CYP2E1, CYP1A2, and CYP2D6 have the most roles in the metabolization of oxidation system. Therefore, it seems that the different results that have been observed in different species may be due to our lack of understanding concerning the inhibitory effects of cimetidine on these cytochromes.

Since this was the first time such a project has been implemented in Iran, it was limited in terms of sample size. It is suggested that higher doses of cimetidine, increasing the frequency of administration within a 24-hour period, or changing the manner of prescribing this drug be evaluated in future studies. It seems that additional studies should be conducted with larger sample sizes to evaluate the relationship between the factors of age, gender, and other factors that affect the determination of the effectiveness of cimetidine.

5. Conclusions

In general, the administration of combination of cimetidine and NAC as therapy for acetaminophen toxicity did not significantly improve the level of the protection of the liver over that of the treatment protocol of NAC alone. It seems that the IV administration of 300 mg of cimetidine IV every six hours is not an adequate dose in the combination with NAC for providing better protection of the liver against acetaminophen toxicity. Thus, changes in manner of the administration of cimetidine and the amounts administered should be evaluated in future studies.

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Conflict of Interest:

There is no conflict of interest to be declared.

Authors' contributions:

All authors contributed to this project and article equally. All authors read and approved the final manuscript.

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