International Pharmacy Acta. 2024; 7(1): e3
Original Research Article
OPEN ACCESS
ISSN: 2645-3266

# Comparison of Two-Bag and Three-Bag N-acetyl cysteine Treatment Protocols in Acute Acetaminophen Poisoning: A Quasi-Experimental Study

Ideh Baradaran Kayal[a], Mohammad Javad Zarei[a], Mitra Rahimi[b], Babak Mostafazadeh[b], Peyman Erfan Talab Evini[b], Shahin Shadnia[b]*

a. School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
b. Toxicological Research Center, Excellence Center of Clinical Toxicology, Department of Clinical Toxicology, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

**Article Info:**
Received: June 2024
Accepted: September 2024
Published online: September 2024

* **Corresponding Author:**
Shahin Shadnia
Email:
shahin1380@gmail.com

**ABSTRACT:**

Acetaminophen poisoning is a major medical challenge requiring effective interventions. N-acetyl cysteine (NAC) is a commonly used antidote. While the FDA has approved the three-bag method, some sources suggest that the two-stage treatment offers comparable effectiveness in preventing liver damage, resulting in fewer adverse reactions, a lower risk of anaphylaxis, and more flexibility in timing adjustments. This study aimed to compare the clinical outcomes and adverse effects of the two-bag and three-bag NAC prescription methods in individuals with acetaminophen poisoning. In this prospective, double-blind, quasi-experimental study, patients with paracetamol overdose who required NAC (N-acetylcysteine) treatment over a one-year period at Loghman Hakim Hospital in Tehran were included. The two-bag regimen consisted of a loading dose followed by a maintenance dose, while the three-bag regimen included three separate doses. Clinical parameters such as blood levels of aspartate aminotransferase (AST), alanine transaminase (ALT), and alkaline phosphatase (ALP), along with demographic data (age, gender) and poisoning characteristics (ingested dose, blood acetaminophen levels, time of overdose), as well as adverse reactions to NAC, were examined. A total of 61 patients participated in the two-bag group and 49 people in the three-bag group. A significant decrease was found in AST in both groups ($p < 0.05$) compared to the time of arrival, and a significant decrease in ALP was seen only in the two-bag group ($p = 0.007$). No cases of hepatotoxicity or acute liver injury were observed. The two groups had no significant difference in the average NAC consumed and the patients' adverse reaction to NAC. The initial and discharge levels of liver enzymes ALT, AST, and ALP did not show a statistically significant difference between the two groups. The two-bag method may be a viable alternative to the traditional three-bag method, as it can ease the workload for ward nurses and has not resulted in any reported deaths.

**Keywords:** Acetaminophen, Poisoning, Acetylcysteine, Medication Therapy Management.

**Please Cite this article as:** Baradaran Kayal I, Zarei MJ, Rahimi M, Mostafazadeh B, Erfan Talab Evini P, Shadnia Sh. Comparison of Two-Bag and Three-Bag N-acetyl cysteine Treatment Protocols in Acute Acetaminophen Poisoning: A Quasi-Experimental Study. Int. Pharm. Acta. 2024; 7(1): e3.
DOI: https://doi.org/10.22037/Ipa.v7i1.45643

## 1. Introduction

Acetaminophen abuse is the main cause of drug poisoning in developed countries, and its incidence is increasing in developing countries as well (1, 2). In 53% of cases, acetaminophen overdose leads to acute liver failure, which affects about 1,000 patients in the United States each year. The main and recommended approach to the treatment of acetaminophen poisoning is the administration of N-acetylcysteine (2-4). A significant problem with NAC therapy is the considerable number of patients who experience adverse reactions to the initial

injection of the loading dose. These reactions are usually non-anaphylactic. Allergic reactions occur within 15 minutes to an hour after receiving the loading dose. In addition, these side effects can lead to treatment discontinuation and premature discontinuation of NAC (5, 6). Previous studies have shown that administering an initial loading dose within two hours can reduce the incidence of NAC-related side effects (3, 7-9). Recent studies involving large numbers of patients have shown that the use of a regimen of two bags of NAC over 20 hours, with an initial intravenous loading dose followed by a slower infusion, can reduce the incidence of secondary side effects. This approach has been compared with the traditional three-bag method, which corresponds to the same total dose in a comparable period, emphasizing its effectiveness in the treatment of non-allergic anaphylactic reactions (10-14).

The three-bag method involves administering 150 mg/kg NAC in 200 ml over 1 hour, followed by 50 mg/kg over 4 hours, and finally 100 mg/kg over 16 hours (15). The two-bag NAC regimen involves administering 200 mg/kg over 4 hours, followed by 100 mg/kg over 16 hours (13). Although several studies have investigated the effectiveness of the two-bag regimen compared to the three-bag regimen, more data is required to draw definitive conclusions regarding the efficacy of the two-bag regimen in comparison to the traditional three-bag method (12). Despite FDA approval of the three-bag method, debates regarding standardized treatment protocols continue (15). Some sources argue that the two-step regimen offers equivalent efficiency in preventing liver injury, resulting in fewer side effects, a lower risk of anaphylaxis, and greater flexibility in timing (11-13). The 2NAC study, the most extensive research on this topic, has shown that both treatments are equally effective in preventing liver damage and reported fewer side effects (12).

Given the high prevalence of acetaminophen poisoning and the large number of hospitalized patients in Iran, no study has yet been conducted comparing the two-bag method with the three-bag method. Additionally, most of the existing studies have compared the incidence of side effects, medical errors, and length of hospital stay. Besides adverse effects, we also examined the efficacy of the regimens in reducing liver enzymes. Therefore, this study aims to evaluate the effectiveness and adverse effects of the two-step method compared to the three-step method.

## 2. Materials and Methods

### 2.1 Study design and setting

This study was a prospective, double-blind, and quasi-experimental study conducted on people who were poisoned with a toxic dose of acetaminophen and had high blood levels of acetaminophen who needed acetylcysteine referred to Loghman Hakim Hospital, Tehran, Iran, during March 2022- March 2023.

### 2.2 Participants

Based on a similar study (14) with a standard difference of 0.85, and considering a 95% confidence interval and 80% power, using Altman's nomogram and factoring in a 15% dropout rate, 101 cases were needed. The study included all hospitalized adult patients with acute paracetamol overdose with a toxic dose (above 7.5 g) who require acetylcysteine for treatment and patients with a paracetamol concentration of more than 150 mg/L four hours after overdose. Patients who did not consent to continue the study were excluded. Those who did not need NAC treatment, patients ate lower dose or their paracetamol concentration was below 150 mg/L four hours after overdose were excluded from the study.

### 2.3 Data collection

For the diagnosis of acute single poisoning with acetaminophen within 24 hours, the modified Rumack-Matthew nomogram was used with a treatment threshold based on a paracetamol concentration of more than 150 mg/L four hours after overdose.

The following information was gathered: the patient's age and gender, the type of paracetamol product and its formula, the dosage of paracetamol, total acetylcysteine dosage, any adverse reactions to acetylcysteine , the time from poisoning to receiving acetylcysteine, mortality, type of poisoning (intentional, post-treatment, accidental), paracetamol concentration upon admission, initial and discharge levels of alanine transaminase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP), and non-allergic anaphylactic or allergic reactions due to prescribed acetylcysteine. The physician documented any adverse events after injection NAC.

### 2.4 Intervention

A double-blind method was used for randomization. The treatment regime was concealed in opaque sealed envelopes labeled 'A' for two-bag and 'B' for three-bag. An objective administrator not involved in patient care randomly selected these envelopes. No one knew their assigned group, eliminating the potential for bias. NAC administration regimens include:

Two-bag IV acetylcysteine regimen: Administer 200 mg/kg over four hours followed by 100 mg/kg over 16 hours.

- Three-bag IV acetylcysteine regimen: Administer 150 mg/kg in 200 ml over 1 hour, then 50 mg/kg over 4 hours, and finally 100 mg/kg over 16 hours.

### 2.5 Statistical Analysis

SPSS software version 21 was utilized for data analysis. The normality of the population was evaluated using the Kolmogorov-Smirnov test. Independent and paired t-tests were applied for parametric data, while Chi-square and Mann-Whitney U test were used for non-parametric data. A significance level of $p<0.05$ was considered. Pearson correlation was employed to explore potential correlations between various continuous variables.

## 3. Results and Discussion

Sixty-one individuals participated in the two-bag group, comprising 30 men and 31 women. On the other hand, the three-bag group consisted of 21 men and 28 women. The age distribution of the Two Bag NAC Prescription group ranged from 19 to 45 years, with an average age of 35.17±5.08 years. The Three Bag NAC Prescription group included participants aged 21 to 54, with an average age of 34.84±4.26 years. The two groups did not show any statistically significant difference in terms of age and sex. No statistically significant difference was found between the two groups in the initial levels or during the discharge of liver enzymes ALT, AST, and ALP (Table 1 and 2).

In terms of drug intake, no significant difference was observed in the two groups, the amount of acetaminophen consumed, the patient's weight, the time gap between drug intake and initial tests, and the acetaminophen serum level. In the two-bag group, 98.4% (60 people) had taken acetaminophen in a suicide attempt, while in the three-bag group, 93.9% (46 people) had done the same. After reviewing the patients' histories, the researchers found that in the two-bag group, 1.69% (one person) consumed alcohol, 8.03% (five people) smoked, and 3.38% (two people) had a drug addiction. In the three-bag group, 14.26% (seven people) smoked, and 2.04% (one person) consumed alcohol. In the two-bag group, one person had depression (1.69%) and one person had hyperthyroidism (1.69%), while in the three-bag group, one person had hyperthyroidism (2.04%) and two people had depression (4.08%). One person in the three-bag group died, and the other patients recovered. No deaths were observed in the two-bag group.

In the two-bag group, 23 people (37.7%) had erythema with urticarial, 27 people (44.3%) had no symptoms, and no case of anaphylactic shock was observed. In the three-bag group, 13 people (26.5%) had erythema with urticaria, 21 people (42.9%) had no adverse event, one case of anaphylactic shock was observed, and three people (6.125%) only had a headache. The mean total amount of NAC administered in the two-bag group was 4.61±0.6 grams, while in the three-bag group, it was 5.6±0.8 grams. There was no significant difference between the two groups in the average NAC consumed and adverse reactions of patients to NAC.

The results of the paired t-test showed a significant decrease in AST in both groups ($p<0.05$), and a significant decrease in ALP was seen only in the two-bag group ($p=0.007$). No significant difference was observed in the two groups' ALT levels at the initial and discharge times. No cases of hepatotoxicity (ALT above 1000

**Table 1.** Comparison of Study Variables Between Two and Three-Bag Group**.**

| | Method of NAC Prescription | | |
|---|---|---|---|
| | Two-Bag | Three-Bag | P-value |
| | Mean±SD / N (%) | Mean±SD/ N(%) | |
| Total number | 61 | 49 | - |
| Gender, female | 31 (50.8%) | 28 (57.1%) | 0.69 |
| Age, year | 35.17±20.08 | 34.84±22.26 | 0.50 |
| Ingested acetaminophen dose (gr) | 10.67±5.9 | 10.52±6.2 | 0.89 |
| Weight of patient (kg) | 66.51±14.04 | 63.98±10.05 | 0.29 |
| Blood acetaminophen levels (gr/ml) | 61.64±68.7 | 69.54±68.8 | 0.55 |
| Initial AST level (U/L) | 31.1±24.7 | 29.7±18 | 0.72 |
| Initial ALT level (U/L) | 23.07±18.8 | 22.96±19.1 | 0.97 |
| Initial ALP level (U/L) | 167.9±58.7 | 172.6±72.2 | 0.71 |
| Duration between consumption and level check (hours) | 5.92±3.3 | 5.8±3.1 | 0.84 |
| Total NAC dose (gr) | 4.61±0.16 | 5.6±0.8 | 0.73 |
| NAC start time (Hours) | 5.07±3.4 | 4.1±2.8 | 0.10 |
| Initial AST level (U/L) | 28.43±25.1 | 25.6±9.4 | 0.45 |
| Initial ALT level (U/L) | 22.97±18.3 | 21.63±16.04 | 0.67 |
| Initial ALP level (U/L) | 161.8±58.2 | 174.8±72.4 | 0.31 |
| Death | 0 | 1 (2.04%) | 0.44 |

Alanine Transaminase (ALT), Aspartate Aminotransferase (AST), Alkaline Phosphatase (ALP), N-Acetyl cysteine (NAC)

**Table 2**. Comparison of the levels of liver enzymes before and after in two groups receiving two bags and three bags of NAC. *P<0.05

| | | Before Treatment | After Treatment | P-value |
|---|---|---|---|---|
| **Two-bag** | AST (U/L) | 31.1±24.7 | 28.43±25.1 | 0.04* |
| | ALT (U/L) | 23.07±18.8 | 22.97±18.3 | 0.92 |
| | ALP (U/L) | 167.9±58.7 | 161.8±58.2 | 0.007* |
| **Three-bag** | AST (U/L) | 29.7±18 | 25.6±9.4 | 0.03* |
| | ALT (U/L) | 22.96±19.1 | 21.63±16.04 | 0.16 |
| | ALP (U/L) | 172.6±72.2 | 174.8±72.4 | 0.62 |

units/liter) and acute liver injury (aminotransferases above 150 units/liter) were observed.

This study was conducted on patients with acetaminophen poisoning to compare the two-bag and three-bag NAC (N-acetylcysteine) regimens.

The results showed no significant difference between the two methods. However, in the two-bag group, no cases of death or anaphylactic shock were observed. In the two-bag regimen, AST and ALP levels showed a significant decrease between, while in the three-bag group, only AST levels decreased significantly. In a study by Wong and Graudins, which examined non-allergic anaphylactic reactions in the two-bag and three-bag regimens, the findings indicated that non-allergic anaphylactic reactions were more frequent in the three-bag regimen compared to the two-bag regimen. However, no significant difference was found between the two methods in terms of gastrointestinal reactions (13). Similarly, in the present study, no significant difference in non-allergic anaphylactic reactions was found between the two groups, possibly due to the limited number of patients in this study. In another study evaluating the effectiveness of the two NAC regimens, the results showed that 3.1% and 2.9% of patients developed acute liver injury (ALI) in the two-bag and three-bag regimens, respectively, 4 to 8 hours after the overdose. The incidence of liver toxicity was 1.2% and 1.6% in the two-bag and three-bag regimens, respectively. Additionally, 21% and 23% of patients in the two-bag and three-bag regimens developed ALI, respectively. This study demonstrated fewer non-allergic anaphylactic reactions in the two-bag regimen, affecting both skin and systemic responses (12). Moreover, no cases of liver toxicity or acute liver injury were observed. By the end of the treatment, the average ALT levels in both groups were lower than at the beginning. No significant difference in side effects related to NAC was observed between the two groups. In Syafiraa et al.'s study on these two regimens, slight differences in elevated ALT levels, liver toxicity, and acute liver injury were reported, although these differences were minor (14). None of these conditions were found in our study. The present study did not report any significant statistical differences in liver enzyme levels or side effects between the two NAC regimens. In contrast, in O'Callaghan et al.'s study, the two-bag regimen was associated with significantly shorter delays during the IV administration of NAC compared to the three-bag regimen. Notably, non-allergic anaphylactic reactions were more common in the three-bag group and were associated with longer delays (16). Daoud et al.'s study found that 6.0% of admissions experienced anaphylactic reactions. The two-bag regimen was associated with fewer anaphylactic reactions (17). This study did not find any cases of anaphylactic shock in the two-bag group, and only one case was observed in the three-bag group, which was not statistically significant. Schmidt et al. observed that the two-bag group had a lower incidence of non-allergic anaphylactoid reactions (NAARs) (4%) compared to the three-bag group (17%). Liver toxicity occurred in 4% of patients overall, with no significant difference between the groups, and there were no serious outcomes. Patients in the two-bag group experienced fewer interruptions or delays (5%) compared to the three-bag group (12%). Medication errors were reported in only 1% of cases (18). Our study also did not find any cases of anaphylactic shock in the two-bag group, with only one case in the three-bag group, which was not statistically significant. No fatalities were reported. A systematic review of the two regimens showed that the two-bag NAC regimen seems to provide similar outcomes to the traditional three-bag regimen in preventing liver injury in patients with acetaminophen poisoning, but with fewer side effects, fewer treatments for adverse events, and fewer interruptions in antidote therapy (19). In our study, no cases of death or anaphylactic shock were observed in the two-bag group, and significant reductions in AST and ALP levels were seen before and after treatment.

Sudanagunta et al. reported the following findings from a study on the two NAC regimens in pediatric acetaminophen poisoning. A total of 243 patients were studied. No difference was found in overall NAARs (p =

0.54). Fewer non-allergic skin anaphylactoid reactions were seen in the two-bag group (3 vs. 15, p = 0.02). Medication errors were significantly reduced in the two-bag regimen (21 vs. 59, p = 0.01). There was no statistical difference in length of stay, ICU admission, transplantation, or death (11). In our study, no deaths or anaphylactic shock cases were observed in the two-bag group, and no cases of liver toxicity were reported.
Kathryn A. Glass reported that NAAR was diagnosed in 11 patients, with no difference between groups. Similarly, no difference in acute liver injury was observed. Prescription errors were significantly lower in the two-bag group (OR 0.24) after adjustment for confounding factors (20). McNulty also concluded that there were fewer anaphylactoid reactions (itching, rash, and swelling) with the two-bag regimen, less use of antihistamines in the two-bag group, and no difference in the incidence of liver toxicity (21). Similarly, in our study, no significant differences between the two methods were found. No deaths or anaphylactic shock cases were observed in the two-bag group, and no cases of liver toxicity or acute liver injury were detected.
The sample size for some specific adverse events was small, potentially affecting the robustness of the present findings. Moreover, the study focused on specific criteria for hepatotoxicity, and other potential markers of liver function were not comprehensively examined. The study also relied on data from patient records, which might introduce variations in the accuracy and completeness of information. Ultimately, external factors such as variations in patient management protocols or treatment practices might have influenced our results.

## 4. Conclusion

Comparison of patient parameters in both methods did not show a significant difference in their effectiveness, and the two-bag method performed similarly to the three-bag method. The two-bag treatment also resulted in a significant reduction in AST and ALP levels after treatment, while the three-bag method significantly reduced AST levels only. Regarding the reduction of allergic and non-allergic reactions and the lack of significant liver toxicity in the two-bag method in most studies, as well as the reduction in patient hospitalization duration and medical errors, the two-bag method appears to be a suitable alternative to the traditional three-bag method. It can reduce the workload for nursing staff and lead to fewer complications and lower mortality rates.

## Acknowledgements

The authors would like to thank the Toxicological Research Center (TRC) of Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran for their support, cooperation, and assistance throughout the study.

## Conflict of interest

There is no conflict of interest.

## Ethics

The study protocol was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences with the code IR.SBMU.RETECH.REC.1400.1039. Participants signed informed written consent forms.

## Authors' ORCIDs

Ideh Baradaran Kayal:
https://orcid.org/0000-0003-4915-4513
Mohammad Javad Zarei:
https://orcid.org/0000-0001-9884-5113
Mitra Rahimi:
https://orcid.org/0000-0002-8785-8207
Babak Mostafazadeh:
https://orcid.org/0000-0003-4872-9610
Peyman Erfan Talab Evini:
https://orcid.org/0000-0002-0995-4973
Shahin Shadnia:
https://orcid.org/0000-0002-9401-0781

## References

[1] Vale JA, Meredith TJ, Goulding R. Treatment of acetaminophen poisoning: the use of oral methionine. Archives of Internal Medicine. 1981;141(3):394-6.
[2] Dart RC, Erdman AR, Olson KR, Christianson G, Manoguerra AS, Chyka PA, et al. Acetaminophen poisoning: an evidence-based consensus guideline for out-of-hospital management. Clinical Toxicology. 2006;44(1):1-18.
[3] Heard KJ. Acetylcysteine for acetaminophen poisoning. New England Journal of Medicine. 2008;359(3):285-92.
[4] Baum RA, Woolum JA, Bailey AM, Howell MM, Weant KA, Geraghty L, et al. Evaluation of dosing strategies of N-acetylcysteine for acetaminophen toxicity in patients greater than 100 kilograms: should the dosage cap be used? Journal of Medical Toxicology. 2021;17:241-9.
[5] Akakpo JY, Jaeschke MW, Ramachandran A, Curry SC, Rumack BH, Jaeschke H. Delayed administration of N-acetylcysteine blunts recovery after an acetaminophen overdose unlike 4-methylpyrazole. Archives of toxicology. 2021;95:3377-91.
[6] Ferretti S, Curatola A, Chiaretti A, Graglia B, Gatto A, Capossela L, et al. Early treatment with N-acetylcysteine reduces hepatotoxicity in acute acetaminophen poisoning. Acta Bio-medica: Atenei Parmensis. 2023;94(S1):e2023033-e.
[7] Lewis J, Lim M, Lai L, Mendoza E, Albertson T, Chenoweth J. Evaluation of N-acetylcysteine dose for the treatment of massive acetaminophen ingestion. Clinical Toxicology. 2022;60(4):507-13.
[8] Mahmoudi GA, Astaraki P, Mohtashami AZ, Ahadi M. N-acetylcysteine overdose after acetaminophen poisoning. International medical case reports journal. 2015:65-9.

[9] Khayyat A, Tobwala S, Hart M, Ercal N. N-acetylcysteine amide, a promising antidote for acetaminophen toxicity. Toxicology letters. 2016;241:133-42.
[10] Wong A, Graudins A. N-acetylcysteine regimens for paracetamol overdose: Time for a change? Emergency Medicine Australasia. 2016;28(6):749-51.
[11] Sudanagunta S, Camarena-Michel A, Pennington S, Leonard J, Hoyte C, Wang GS. Comparison of two-bag versus three-bag N-acetylcysteine regimens for pediatric acetaminophen toxicity. Annals of Pharmacotherapy. 2023;57(1):36-43.
[12] Wong A, Isbister G, McNulty R, Isoardi K, Harris K, Chiew A, et al. Efficacy of a two bag acetylcysteine regimen to treat paracetamol overdose (2NAC study). EClinicalMedicine. 2020;20.
[13] Wong A, Graudins A. Simplification of the standard three-bag intravenous acetylcysteine regimen for paracetamol poisoning results in a lower incidence of adverse drug reactions. Clinical toxicology. 2016;54(2):115-9.
[14] Syafira N, Graudins A, Yarema M, Wong A. Comparing development of liver injury using the two versus three bag acetylcysteine regimen despite early treatment in paracetamol overdose. Clinical Toxicology. 2022;60(4):478-85.
[15] Otten EJ. Goldfrank's Toxicologic Emergencies. Journal of Emergency Medicine. 2012;42(2):239-40.
[16] O'Callaghan C, Graudins A, Wong A. A two-bag acetylcysteine regimen is associated with shorter delays and interruptions in the treatment of paracetamol overdose. Clinical Toxicology. 2022;60(3):319-23.
[17] Daoud A, Dalhoff KP, Christensen MB, Bøgevig S, Petersen TS. Two-bag intravenous N-acetylcysteine, antihistamine pretreatment and high plasma paracetamol levels are associated with a lower incidence of anaphylactoid reactions to N-acetylcysteine. Clinical Toxicology. 2020;58(7):698-704.
[18] Schmidt LE, Rasmussen DN, Petersen TS, Macias-Perez IM, Pavliv L, Kaelin B, et al. Fewer adverse effects associated with a modified two-bag intravenous acetylcysteine protocol compared to traditional three-bag regimen in paracetamol overdose. Clinical toxicology. 2018;56(11):1128-34.
[19] Cole JB, Oakland CL, Lee SC, Considine KA, Rudis MI, Swanson AL, et al. Is Two Better Than Three? A Systematic Review of Two-bag Intravenous N-acetylcysteine Regimens for Acetaminophen Poisoning. Western Journal of Emergency Medicine. 2023;24(6):1131.
[20] Glass KA, Stoecker ZR, LeRoy J, Palmer CL, Stipek J, Boley S. Investigating a Novel Two-Bag N-Acetylcysteine Regimen for Acetaminophen Toxicity. Journal of Medical Toxicology. 2024:1-8.
[21] McNulty R, Lim JME, Chandru P, Gunja N. Fewer adverse effects with a modified two-bag acetylcysteine protocol in paracetamol overdose. Clinical toxicology. 2018;56(7):618-21.