

Intravenous acetylcysteine versus oral and intravenous acetylcysteine: Does a combination therapy decrease side effects of acetylcysteine?

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ABSTRACT

Objective: Acetylcysteine (NAC) is the antidote for acetaminophen toxicity given by two routes (intravenous or orally). Both routes have adverse side effects. We applied a new protocol using the combination therapy of both the oral and IV route for each patient and compared it with the only IV administration therapy regarding the outcome including anaphylactoid reactions.

Methodology: A Randomized clinical trial study was performed on acetaminophen poisoning patients. The group A (IV group) was managed by initial bolus of IV NAC with 150 mg/kg infused in 200cc of 5% dextrose in water within 30 minutes, followed by a 4 hour infusion of 50 mg/kg of NAC in 500cc of 5%DW and finally with a 16 hour infusion of 100 mg/kg NAC in 1000cc 5%DW. In group B (oral + IV group), Initial NAC 140 mg/kg in 200cc of 5%DW was given orally. Then the administration of NAC was continued by IV route 50 mg/kg in 500cc of 5%DW in four hour infusion and then IV route, 100 mg/kg in 1000cc of 5%DW in 16 hour infusion. Anaphylactoid and anaphylaxis reaction were compared between two groups.

Results: Fifty patients were evaluated. Anaphylactoid reaction was observed in 60.7% and 13.3% in A and B group respectively (P value, 0.004). There was a significant relationship between the anaphylactoid reactions and the route of NAC administration (P value, 0.001; r, 0.47).

Conclusion: Less anaphylactoid reactions may be observed in patients who receive combination of oral and intravenous acetylcysteine than the IV administration therapy.

KEY WORDS: Acetaminophen, Poisoning, N-acetylcysteine (NAC), Anaphylaxis, anaphylactoid, Toxicity, Overdose.

doi: [http://dx.doi.org/10.12669/pjms.291\(Suppl\).3522](http://dx.doi.org/10.12669/pjms.291(Suppl).3522)

How to cite this:

Eizadi-Mood N, Sabzghabae AM, Siadat S, Yaraghi A, Shariati M, Gheshlaghi F, et al. Intravenous acetylcysteine versus oral and intravenous acetylcysteine: Does a combination therapy decrease side effects of acetylcysteine? *Pak J Med Sci* 2013;29(1)Suppl:308-311.

doi: [http://dx.doi.org/10.12669/pjms.291\(Suppl\).3522](http://dx.doi.org/10.12669/pjms.291(Suppl).3522)

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INTRODUCTION

Acetaminophen is a drug that relieves pain and fever and can be found in both prescription and over-the-counter (OTC) products. Acetaminophen toxicity is one of the most common causes of poisoning worldwide.¹

The severity of acetaminophen toxicity varies depending on the dose and whether appropriate treatment is received.² The initial treatment for acetaminophen overdose is gastrointestinal decontamination. In earlier presentations, charcoal can be given when the patient arrives and gastric lavage is considered if the amount ingested is potentially life-threatening.^{2,3}

N-acetylcysteine (NAC) is the antidote for acetaminophen toxicity, reduces morbidity and mortality following acetaminophen poisoning.² The most common adverse effects associated with oral

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acetylcysteine are nausea and vomiting. It is also easy to administer and it has lower cost, but the duration of treatment with the oral route is 72 hours, which may make hospital admission necessary and another disadvantage is about its gastrointestinal intolerance resulting from its foul taste.^{4,5}

However the most advantage of IV route is shortening duration of hospital stay, increasing both doctor and patient convenience, and allowing administration of activated charcoal to reduce absorption of both the acetaminophen and any co-ingested drugs without concerns about interference with oral acetylcysteine.⁶

The main disadvantages for IV route are its induction of potentially life-threatening anaphylactoid reactions occurring in 4 to 23% of patients and its greater cost.⁷ Adverse drug reactions to intravenous NAC might affect therapeutic outcome or lead to treatment delay.⁸ The most common are anaphylactoid reactions including rash, pruritus, angioedema, nausea and vomiting, bronchospasm, tachycardia, and hypotension. Other adverse effects are headache, chest pain, dizziness and convulsion. Rarely, severe life-threatening reactions may occur in predisposed individuals, such as patients with asthma.^{9,10}

In some countries NAC is given intravenously and in others orally. Intravenous (IV) and oral administration are considered to be equally effective in practice. However, IV is the only recommended route in Australasian and British practice.¹¹

In our referral poisoning emergency department the accepted route of NAC administration is the intravenous route. In a previous study in our hospital, anaphylactoid reactions following intravenous NAC was found to be high, although there was no anaphylactoid shock or death. Moreover the oral route was not acceptable in our patients because refractory emesis frequently led to delayed or ineffective administration of the antidote. Also discharging the patients with their own decision makes the physician worry about getting oral NAC correctly. Therefore we applied a new protocol using the combination therapy of both the oral and IV route for each patient and compared it with the only IV administration therapy regarding the outcome including anaphylactoid reactions. By this combination method using first initial oral administration we may reduce the anaphylactoid or anaphylaxis reaction as well as reduce the length of hospital stay.

METHODOLOGY

A randomized clinical trial was conducted from April 2009 to September 2010 in Poisoning Emer-

gency Department of our hospital, a poisoning referral department in our province. The study was reviewed and approved by local ethics committee (IRCT201112146948N2). The inclusion criteria were patients with acetaminophen poisoning aged ≥ 18 yr, with the time from ingestion to admission less than eight hours.

The exclusion criteria were patients who vomit two times after oral NAC was given (these patients were excluded and were managed with IV NAC only), pregnant patients and those who had risk factors for hepatic toxicity (e.g. those who had hepatic cirrhosis, chronic ethanol ingestion, usage of substances that induce cytochrome P450 enzyme activity including rifampin, phenobarbital, isoniazid, phenytoin and carbamazepine).

Based on local guideline if the time from acetaminophen ingestion to patient admission was less than four hours, gastric evacuation and charcoal 1 g/kg in 200cc water were administered. Four hours after acetaminophen ingestion blood serum was given to assess the patient's serum acetaminophen level. For patients arriving between 4-8 hours after acetaminophen ingestion blood sample was given from each patient to evaluate patient's serum acetaminophen level.

Blood samples were also evaluated for liver function tests; total and direct bilirubin, alanine transaminase (ALT), aspartate aminotransferase (AST), partial thromboplastin time (PTT), prothrombin time (PT), international normalized ratio (INR); renal tests (creatinine, urea), and also for sodium (Na) and potassium (K).

A written consent form was taken from the accompanying person. Then the patients allocated in two groups randomly. First group (group A) received only intravenous NAC, while the second group (group B) received both IV and oral NAC.

The group A (IV group) was managed by IV NAC with 150 mg/kg infused in 200cc of 5% dextrose in water (5%DW) in 30 minutes, followed by a 4 hour infusion of 50 mg/kg of NAC in 500cc of 5%DW and finally with a 16 hour infusion of 100 mg/kg NAC in 1000cc 5%DW.

In group B (oral + IV group), initial NAC 140 mg/kg in 200cc of 5%DW was given orally. Then the administration of NAC was continued by IV route 50 mg/kg in 500cc of 5%DW in four hour infusion and then IV route, 100 mg/kg in 1000cc of 5%DW in 16 hour infusion. If vomiting occurred in any patient during one hour after the ingestion of the oral NAC then 10 mg metoclopramide was given IM and the oral NAC was given with the same dose again.

Table-I: Comparative Evaluation of different variables in acetaminophen poisoned patients.

	Group A	Group B	P value
Acetaminophen ingested (mg)	12337.5 ± 1091.44	11290 ± 688.8	0.51
Time from ingestion to admission	4.78 ± 0.89	3.53 ± 0.75	0.36

Group A: patients who received intravenous (IV) N-Acetylcysteine (NAC);

Group B: patients received both initial oral and then IV NAC.

Patient's vital signs were monitored and also patients were controlled for signs of anaphylactoid reactions. If any signs and symptoms of nausea, vomiting, flushing, dyspnea, pruritus, erythema, dizziness, urticaria, hypotension or anaphylactic shock happened then the infusion was stopped, a prepared check list was completed and symptomatic treatment with antihistamines or steroids or bronchodilators was started. Then the NAC infusion was restarted but with a slower rate.

When the infusion was over, a psychologist visited each patient, then the patient was discharged and 48-72 hours after discharge the patients were checked for liver function tests and renal tests again. In our hospital oral NAC was in the form of a 600 mg tablet named Flumucil® and in a 2g ampoule named Parvolex®.

Data was collected through a check list. SPSS 17.0 were used as the statistical software. Chi-square, concise Fisher test, Cochran test, independent t-test and Spearman test were applied where applicable. P value less than 0.05 was considered statistically significant.

RESULTS

There were 50 patients with acetaminophen toxicity referred to our hospital during the study period. Patients were divided randomly as group A (25 patients) and group B (25 patients). 10 patients of the group B were excluded from our study.

The average (SD) of age among group A was 23.78 ± 0.88 and for group B it was 24.46 ± 1.06 (P value, 0.64). 17.9% of group A and none of group B had a history of psychological problems (P value,

0.14). There was no significant difference in the amount of acetaminophen ingested and the time from ingestion to admission to the hospital (Table-I).

In group A, 60.7% had vomited before being referred to the hospital and in group B, 26.7% had vomited (P value, 0.06). 42.3% of group A had ingested another drug with acetaminophen and in group B it was 60% (P value, 0.34).

Before NAC administration, 71.4% of the patients in group A and 28.6% in group B had a combination of more than one symptom such as nausea, vomiting, dizziness, headache and confusion. Three patients had loss of consciousness (Table-II).

After NAC administration, in group A, 60.7% and 13.3% of group B showed at least one sign of anaphylactoid reaction (P value, 0.004). Table-III demonstrates the frequency of each sign or symptom after administration of IV NAC.

In group A, 3.6% and in group B no patient had history of anaphylactoid reactions (P value, 1). Spearman correlation test showed no significant relationship between past history of sensitivity and anaphylactoid reactions (P value, 0.33). However there was a significant relationship between the anaphylactoid reactions and the route of NAC administration (P value, 0.001; r, 0.47).

DISCUSSION

Oral N-acetylcysteine is associated with nausea and vomiting in 50% of acetaminophen poisoned patients.⁵ On the other hand, intravenous NAC is the only recommended route in some countries.

Table-III: Frequency of each sign or symptom after administration of NAC in two different groups of acetaminophen poisoning.

Signs and Symptoms	Group A	Group B	P value
No sign or symptom	39.3%	86.7%	0.004
Nausea and vomiting	28.5%	13.3%	0.45
Dyspnea	3.6%	0%	1
Flushing	3.6%	0%	0.53
More than one symptom*	25%	0%	0.01

*more than one symptom except nausea and vomiting, including pruritus, dyspnea, flushing and coughing.

Group A: patients who received intravenous (IV) N-Acetylcysteine (NAC); Group B: patients received both initial oral and then IV NAC.

Table-II: Signs and symptoms of poisoning before NAC administration in two different groups.

Signs and Symptoms	Group A	Group B	P value
No sign or symptom	10.7%	40%	0.04
Nausea and vomiting	10.7%	20%	0.64
Dizziness	3.6%	0%	1
Sleepiness	3.6%	13.3%	0.54
More than one symptom	71.4%	26.7%	0.009

Group A: patients who received intravenous (IV) N-Acetylcysteine (NAC); Group B: patients received both initial oral and then IV NAC.

Anaphylactoid reactions was found in 14.9%¹² 48.4%¹³ and 46.7%¹⁴ of the patients and potentially life-threatening anaphylactoid reactions has been reported in 4 to 23% of patients in different studies.^{7,10,15-18}

In our study the anaphylactoid reaction was observed overall in 44.2% of the patients (13.3% in patients received IV NAC, versus 60.7% of patients both initial oral and then IV NAC).

In group A (IV group), the reactions were nausea, vomiting, flushing, dyspnea, and headache, but in group B (oral + IV group), nausea and vomiting were reported. These reactions are seen in other studies using intravenous NAC. In Pakravan's study in 2008 the reactions were nausea (70.4%), vomiting (60.4%), flushing (20.9%), pruritus (20.1%), dyspnea (13.6%) and dizziness in 7.7% of the patients.¹⁹ In Zyoud's study in 2010, 67.6% had adverse reactions after infusion of NAC. This study suggests that late time to NAC infusion is a risk factor for developing cutaneous anaphylactoid reactions but not for other type of reactions.¹⁴

Some scientists believe that treating acetaminophen overdose is best keeping in view the patients arrival time in the hospital. If a patient arrives before eight hour after acetaminophen ingestion then it's better to use intravenous NAC, but if a patient arrives later, then oral NAC would be the best option. In Mehrpour's study in 2011 they suggest that even in late phases of intoxication high-dose intravenous NAC can serve a substantial improvement.²⁰

In conclusion, in our new protocol less anaphylactoid reactions was observed in patients received combination of oral and intravenous acetylcysteine than the IV administration therapy.

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Authors Contribution:

All authors were involved in design, coordinated in the study, run all modeling studies and prepared the manuscript. All authors have read and approved the final version of the manuscript.

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