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
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.8,9

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 Emergency 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/k 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.
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 Fluimucil® 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, Cochrane 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. 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.

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Anaphylactoid reactions was found in 14.9%\textsuperscript{12} 48.4%\textsuperscript{13} and 46.7%\textsuperscript{14} of the patients and potentially life-threatening anaphylactoid reactions has been reported in 4 to 23% of patients in different studies.\textsuperscript{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%), pruriitus (20.1%), dyspnea (13.6%) and dizziness in 7.7% of the patients.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.

**REFERENCES**

1. Gunnell D, Murray V, Hawton K. Use of paracetamol (acetaminophen) for suicide & nonfatal poisoning: worldwide patterns of use and misuse. Suicide Life Threat Behav. 2003;30(4):313-326.

2. Daly FFS, Fountain JS, Murray L, Graudins A, Buckley NA. Guidelines for the management of paracetamol poisoning in Australia and New Zealand-explanation and elaboration. A consensus statement from clinical toxicologists consulting to the Australasian poisons information centers. Med J Aust. 2008;188(5):296-301.

3. Vale JA, Kulig K. Position paper: gastric lavage. J Toxicol Clin Toxicol. 2004;42(7):933-943.

4. Ternullo S. Acetadote (intravenous acetylcysteine): adverse effects more significant than with oral acetylcysteine. J Emerg Nurs. 2006;32(1):98-100.

5. Kao LW, Kirk MA, Furbee RB, Mehta NH, Skinner JR, Brizendine EJ. What is the rate of adverse events after oral N-acetylcysteine administered by the intravenous route to patients with suspected acetaminophen poisoning? Ann Emerg Med. 2003;42(6):741-750.

6. Buckley N, Whyte IM, O’Connell D, Dawson AH. Oral or intravenous N-acetylcysteine: which is the treatment of choice for acetaminophen (paracetamol) poisoning? J Toxicol Clin Toxicol. 1999;37(6):759-767.

7. Buckley N, Eddleston M. Paracetamol (acetaminophen) poisoning. Clin Evid. 2005;14:1738–1744.

8. Sandilands EA, Bateman DN. Adverse reactions associated with acetylcysteine. Clin Toxicol (Phila). 2000;47(2):81-88.

9. Appelboom AV, Dargan PI, Knighton J. Fatal anaphylactoid reaction to N-acetylcysteine: caution in patients with asthma. Emerg Med J. 2002;19(6):594-595.

10. Schmidt LE, Dalhoff K. Risk factors in the development of adverse reactions to N-acetylcysteine in patients with paracetamol poisoning. Br J Clin Pharmacol. 2001;51(1):87–91.

11. Selvan VA, Calvert SH, Cavell G, Glucksman E, Kerins M, Gonzalez J. Weight-based N-acetylcysteine dosing chart to minimise the risk of calculation errors in prescribing and preparing N-acetylcysteine infusions for adults presenting with paracetamol overdose in the emergency department. Emerg Med J. 2007;24(7):482-484.

12. Waring WS, Stephen AF, Robinson OD, Dow MA, Pettie JM. Lower incidence of anaphylactoid reactions to N-acetylcysteine in patients with high acetaminophen concentrations after overdose Clin Toxicol (Phila). 2008;46(6):496-500.

13. Lynch RM, Robertson R. Anaphylactoid reactions to intravenous N-acetylcysteine: a prospective case controlled study. Accid Emerg Nurs. 2004;12(1):10-15.

14. Zyoud SH, Awang R, Syed Sulaiman SA, Swelih WM, Al-Jabi SW. Incidence of adverse drug reactions induced by N-acetylcysteine in patients with acetaminophen overdose. Hum Exp Toxicol. 2010;29(3):153-160.

15. Lifshutz M, Komemhol P, Reuveni H. The incidence and nature of adverse reactions during intravenous acetylcysteine therapy for acetaminophen overdose. J Pharm Technol. 2000;16:47-49.

16. Prescott L. Oral or Intravenous N-Acetylcysteine for Aceta-minophen Poisoning? Ann Emerg Med. 2005;45(4):409-413.

17. Mant T, Tempowski JH, Volans GN, Talbot JC. Adverse reactions to acetylcysteine and effects of overdose. Br Med J (Clin Res Ed). 1984;289(6439):217-219.

18. Bailey B, McGuigan MA. Management of anaphylactoid reactions to intravenous N-acetylcysteine. Ann Emerg Med. 1996;31(6):710-715.

19. Pakravan N, Waring WS, Sharma S, Ludlam C, Meeson I, Bateman DN. Risk factors and mechanisms of anaphylactoid reactions to acetylcysteine in acetaminophen overdose. Clin Toxicol (Phila). 2008;46(8):697-702.

20. Mehrpour O, Shadnia S, Saraye-Zadeh H. Late extensive intravenous administration of N-acetylcysteine can reverse hepatic failure in acetaminophen overdose. Hum Exp Toxicol. 2011;30(1):51-54.

**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.