

Evaluation of Prothrombin Time in Acute Acetaminophen Overdose treated by N-acetylcysteine

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Abstract

Background: Acetaminophen (N-Acetyl-p aminophenol; APAP) is one of the most common types of analgesics. It is also the most common xenobiotic reported to poison centers. This study investigates if therapeutic doses of NAC can falsely increase coagulation tests, prothrombin time (PT) and bleeding time (BT).

Methods: Thirty-six APAP poisoned patients whose acetaminophen serum concentration were in toxic zone in the Rumack-Matthew graph were treated by NAC according to standard intravenous 21 hours protocol. Prothrombin time (PT) and bleeding time (BT) in all cases were measured before the start of the NAC and at the 8th and 16th hour of the treatment.

Results: The mean age of the cases was 21.5 ± 5.12 years old. Among them, 31 cases (86%) were female. The mean dose of ingested APAP was 9.6 ± 2.0 grams (7.8 – 16.1 g). Mean of SLA was 196.0 ± 37.7 . The means of BT were not significantly different at all evolution times (2.6 ± 0.64 , 2.6 ± 0.62 and 2.6 ± 0.6). The means of PT rose at 16th hour of NAC treatment in as compared 8th hour (16.1 ± 1.1 s 12.3 ± 0.6 s, respectively) ($P < 0.001$).

Conclusion: With specific reference to our study results, a low level of rising PT resulting from an NAC treatment is not a reliable indicator of liver damage. Further investigation on the effect of NAC on clotting factors is recommended.

Key words: Acetaminophen Poisoning; N-acetylcysteine; Bleeding Time; Prothrombin Time

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INTRODUCTION

Acetaminophen (N-Acetyl-p aminophenol; APAP) is one of the most common types of analgesics. It is also the most common xenobiotic reported to poison centers (1). There are various pharmaceutical forms of APAP, Acetaminophen basis or in combination with other drugs. APAP intoxication frequently happens due to mistaken judgment on the toxicity of the drug (1). The *American Association of Poison Control Centers* in 2008 reported, 71,325 APAP derivatives poisoning incidents and 80,845 cases from APAP. Of these, there were 59 and 69 deaths respectively (2). The toxic doses of APAP in adult and children are 7.5 grams and 150mg/kg respectively (3). Coagulopathy, rising aminotransferase and prothrombin time (PT) occur 24 - 48 hours after ingestion (3, 4). Most patients can be successfully treated if N-acetylcysteine (NAC) is administered within the first 6 hours after acute intoxication (1, 2, 5). The administration of NAC breaks down products of APAP and increases glutathione levels (1, 3, 5). There is some evidence that the administration of NAC could alter the coagulation state of the

patients (1, 4, 6). We investigated whether therapeutic doses of NAC can cause false increased coagulation tests (prothrombin time and bleeding time).

METHODS

For this study, we evaluated coagulation tests in acute APAP poisoned patients referred to the Beheshti University of Medical Sciences' hospitals with NAC treatment in 2013. Our main inclusion criteria were history of acute ingestion of > 7.5 grams APAP during last 24 hours; age > 14 years old. Excluded from the study were patients with a history of chronic APAP consumption, previous history of liver disease, coagulation or platelet disorders and multiple drugs ingestion. The study also excluded patients who had ingested acetaminophen + codeine. However, cases of ingested Adult Cold Tablet (APAP + Chlorpheniramine+ phenylephrine) were not excluded. We collected the following information from each eligible patient: age, gender, bleeding time (BT), prothrombin time (PT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum levels of acetaminophen (SLA). SLAs were measured at least 4 hours

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after ingestion and the levels of APAP toxicity were estimated based on the Rummak-Matheiw graph. As the SLA results were obtained at least 12 hours later, NAC treatment on all patients began before the 8th hour of APAP ingestion independent to SLA results in accordance to the 21- hour standard protocol (150;50 and 100 mg/kg). For all patients with a non-toxic SLA, NAC treatment was discontinued and they were excluded from the study. PT of all cases was evaluated three times, at the start of the NAC treatment and 8 and 16 hours later. BTs were also evaluated as PT according to the Duke Method (7). PT and BT results were analyzed by ANOVA (Tukey's post hoc test) with SPSS 21.

All components of this study were approved by the Ethics Committee of the Research Center of Beheshti University of Medical Science. All participants signed the consent forms.

RESULTS

Of all the APAP poisoned cases referred to our hospital, 36 patients met the required criteria. The mean age of the studied cases was 21.5 ± 5.12 years old. 5 (13.9%) were male and 31 (86.1%) were female. The mean dose of ingested APAP was 9.62 ± 1.98 grams (7.80 – 16.05 g). All patients had attempted suicide. The mean of SLA was 195.94 ± 37.67 mg/dl. This was at toxic level.

The mean of patients' PT rose at 16th hour of the NAC treatment in comparison to the 8th hour ($P < 0.001$). However, we were not able to detect any significant difference between means of PT at the starting time and the 8th hour (Figure 1).

The means of BT were not significantly different before, during and after NAC treatment (2.58 ± 0.64 , 2.57 ± 0.62 and 2.58 ± 0.64 , respectively).

DISCUSSION

This study investigates the effect of NAC on PT and BT in acute intoxicated APAP patients. A study by Thorsen and colleagues had shown that NAC increased the BT by reducing the von Willebrand Factor (8), which is vital for platelet adhesion to the vessel wall. Its dysfunction raises the BT (7). However, our study did not detect any difference on the BT following the NAC administration.

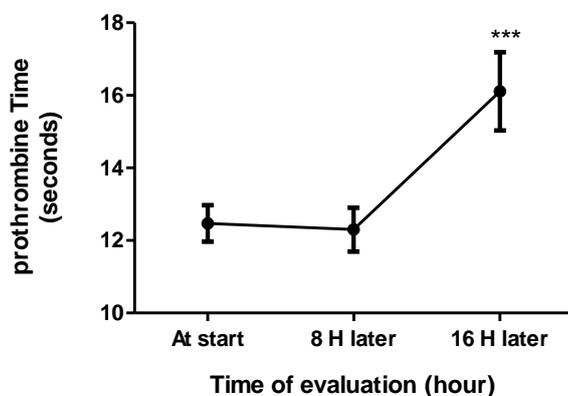


Figure 1. Prothrombin time in acetaminophen poisoned patients treated by N-acetylcysteine, ($P < 0.001$).

Pakravan and co-workers reported a significant fall in plasma vitamin-K dependent clotting factors activity (II, VII, IX, X) following NAC infusion (9). Pizon et al cited that adding

Various concentrations of NAC, 0-1000 mg/l to healthy volunteer serums showed that coagulation factor activity levels of NAC contaminated serums were significantly lower than control. Pizon et al also evaluated the effect of NAC on PT. They reported a dose-dependent effect of NAC on PT in vitro human model (10). In our study, the PT changed in an NAC treatment. However, we did not find any change at the 8th hour. Anthony and colleagues also added various concentration of NAC to serum of healthy persons and reported dose-dependent increasing on PT (10). Evidence of APAP liver toxicity appeared 24 hours later (3). However raising AST is the most sensitive indicator of an APAP liver toxicity, abnormal PT, glucose, bilirubin, lactate and phosphate. PH is more important indicative of liver failure and prognosis than AST or ALT (2, 3, 5).

CONCLUSION

Abnormal PT is one of the most important diagnostic and prognostic factors of *liver damage*. This study investigated the effects of NAC on PT and BT in the first 24 hours after APAP poisoning. Where our results is concerned, a low level rising of PT following NAC treatment is not a reliable indicator of liver damage. Further investigation on the effect of NAC on clotting factors is recommended.

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