*Original Research Article*

Indian Journal of Emergency Medicine
Volume 6 Number 2, April – June 2020
DOI: http://dx.doi.org/10.21088/ijem.2395.311X.6220.4

# Acute Single Deliberate Ingestion of Acetaminophen and Correlation with International Normalized Ratio and Length of Hospital Stay among Patients Visiting the Emergency Department: A Retrospective Study

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**Received on** 14.02.2020
**Accepted on** 16.03.2020

**Abstract**

*Context:* Acetaminophen is an easily available and frequently abused over-the-counter drug both in the western world and India. It is one of the commonest cause of medication-related poisoning in the world. The spectrum of hepatotoxicity associated with Acetaminophen can extend from a mild liver disease to fulminant hepatic failure requiring transplant. The toxic component N-Acetyl-p-benzoquinone imine (NAPQI) causes centri-lobular hepatic necrosis. This study aims to find the predictor of duration of hospital stay in acute acetaminophen overdose. *Aim:* The study aims to find correlation between the amount of ingested Acetaminophen and initial International Normalized Ratio (INR) and the latter with duration of hospital stay among patients visiting the Emergency Medicine department (ED) with a single deliberate ingestion of Acetaminophen. *Materials and Methods: Settings and Design:* This is a retrospective, observational study done among patients presenting to the emergency medicine department in a tertiary care centre in South India with acute single deliberate ingestion of Acetaminophen. Study population belonged to 15-45 years age group. The period of study was during the years 2016-2019. *Subjects and Methods:* Baseline demographics and clinical characteristics were noted. Correlation between ingested Acetaminophen and initial INR within 24 hours of ingestion and between initial INR and duration of hospital stay was analyzed with scatter plot. *Statistical Analysis used:* Statistical analysis was done using IBM SPSS version 23.0 (SPSS Inc., Chicago, USA). The categorical variables are represented as percentages and continuous variables are represented as mean ± standard deviation (SD). To test the statistical significance of association of categorical variables, Pearson correlation coefficient (r) was used. A p-value of $<0.05$ was considered as statistically significant. *Results:* The present study included 52 patients who deliberately ingested acetaminophen, with 13 males (25%) and 39 females (75%) and mean age of 23.67 ± 6.9 years. History of previous psychiatric illness was noted in 23.1% patients. Gastric lavage and activated charcoal was done in 36 (69.2%) and 13 (25%) patients respectively. Ingested amount of Acetaminophen had statistically significant correlation with initial INR with a p-value of 0.004. It was also noticed that the initial INR value and duration of hospital stay had a statistically significant correlation with P-value of $<0.001$. *Conclusion:* The study concludes that there is correlation between the dose of Acetaminophen ingested and INR. INR value also had positive correlation with duration of hospital stay.

**Key words:** International Normalized Ratio; Acetaminophen; Duration of hospital stay, Emergency department.

**How to cite this article:**

Manna Maria Theresa, Prannoy George Mathen, Gireesh Kumar K.P et al. Acute Single Deliberate Ingestion of Acetaminophen and Correlation with International Normalized Ratio and Length of Hospital Stay among Patients Visiting the Emergency Department: A Retrospective Study Indian J Emerg Med 2020;6(2):73–78.

# Introduction

### *Background/Rationale*

Paracetamol; Abenol; Apo-Acetaminophen; Atasol; Novo-Gesic; Pediatrix; Tempra; Tylenol are some of the available combinations of acetaminophen.

Therapeutic dose of Acetaminophen is 4g a day.[1] Repeated therapeutic doses can be hepatotoxic. Acetaminophen is one of the commonest cause of drug-induced liver injury (DILI),[2] and is the most common cause of acute liver failure (ALF) in United States – in 50 percent of all reported cases and approximately 20 percent required liver transplant.[3]

Acetaminophen remains a major cause of overdose-related liver failure.[7] If overdose is identified early mortality rates can be reduced. However, once patient develops acute liver failure, one third of patients require liver transplantation there is 28 percent risk for mortality.[8]

Acetaminophen is absorbed from the gastrointestinal tract (duodenum).[4] Serum acetaminophen concentrations peak between one-half and two hours after an oral therapeutic dose.[5] Peak serum concentrations are reached within four hours after overdose of immediate-release preparations, but may be delayed beyond four hours if coingested with opiates, anticholinergic agents.[6] 10 to 20 mcg/mL (65 to 130 micromol/L) is the therapeutic serum concentration of Acetaminophen.

Elimination half-lives range from two to four hours for most acetaminophen preparations, but the elimination phase may be delayed in extended-release preparations due to prolonged tablet dissolution and absorption.[7,8]

Metabolism of acetaminophen occurs within the hepatic microsomes. At therapeutic doses, 90% of acetaminophen is metabolized in the liver to sulfate and glucuronide conjugates via sulfotransferase (SULT) and UDP-glucuronosyl transferases (UGT) and these conjugated metabolites are then excreted through urine.[20] The remaining acetaminophen is metabolized via oxidation by the hepatic cytochrome P450 into a toxic intermediate N-acetyl-p-benzoquinoneimine (NAPQI).[10-14]

NAPQI arylates and binds covalently to the cysteine groups on hepatic macromolecules like mitochondrial proteins, forming NAPQI-protein adducts when the hepatic glutathione stores depletes more than 70-80 percent.[29-31] This process is irreversible. The formation of these adducts leads to oxidative hepatocyte injury, alteration of the mitochondrial ATP-synthase α-subunit, and hepatocellular necrosis.[15-17] Toxic free radicals (e.g., peroxynitrite) form nitro-tyrosine adducts within the mitochondria.[13,14] Injury to the mitochondrial DNA and ATP-synthase causes cessation of ATP synthesis. Lipid peroxidation and membrane injury play a role in the progression of hepatocellular injury.[12] Along with the release of cytokines, apoptosis-inducing factor (AIF), endonuclease G (EndoG), and reactive nitrogen and oxygen species from damaged mitochondria causes hepatic injury. Cytokine and cellular content release from hepatocytes may initiate a secondary inflammatory response from Kupffer cells and other inflammatory cells, extending the zone of hepatic injury.[18-21] Serum protein adducts, markers of toxicity, have been detected as early as one hour after acetaminophen treatment.[9]

Chronic acetaminophen poisoning is also characterized by markedly elevated aminotransferases (>3000 IU/L), combined with hypovolemia, jaundice, coagulopathy, hypoglycemia, and acute renal failure in greater than 50 percent of these patients. The initial manifestations of acetaminophen poisoning are often mild and nonspecific, and do not reliably predict hepatotoxicity.

Severe overdose can result in liver failure. Thus, measurement of the serum acetaminophen concentration after 4 hours of ingestion is critical whenever overdose is suspected to initiate on N-acetyl cysteine. If the ingestion was more than four hours from the time of presentation, it should be drawn immediately. The Acetaminophen level should be plotted according to the modified Rumack-Matthew normogram to determine the need for NAC therapy.

Acute liver failure refers to the development of severe acute hepatic injury with encephalopathy and impaired synthetic function (INR of ≥1.5) in a patient without preexisting liver disease or cirrhosis.[21]

Existing literature recommends that acetaminophen-induced liver injury is acute in onset, progresses rapidly, is characterized by marked elevation of plasma aminotransferases (often >3000 IU/L), and is associated with a rising prothrombin time/international normalized ratio. This study aims to find a single predictor of length hospital stay at the time of presentation of patients with Acetaminophen overdose.

## Objectives

The primary objective of the study is find correlation between the amount of ingested Acetaminophen and initial International Normalized Ratio (INR). The secondary objective is to correlate the initial International Normalized Ratio (INR) with the duration of hospital stay.

## Materials and Methods

### *Study design*

A retrospective observational study done amoung patients coming to the Emergency Medicine Department of acute single deliberate ingestion of Acetaminophen. The study was approved by the hospital ethics committee (Institutional Review Board).

### *Setting*

The study duration was between January 2016 and December 2019 in the Emergency Medicine department and Emergency Intensive Care Unit (ICU) of a South Indian Medical College Hospital with an annual emergency department patient load of around 50,000.

### *Participants*

Patients with acute single ingestion of actaminophen in the age group 15 to 45 years admitted in the emergency medicine department regardless of the gender, hemodynamic status were included in the study.

***Exclusion criteria***: Coingestion of other toxins, presentation after 24 hours of Acetaminophen ingestion were excluded.

### *Variables*

Quantitative variables–Ingested dose of Acetaminophen measured in Gram, International Normalised Ratio (INR), duration of hospital stay measured in days.

***Study size:*** Out of the 78 subjects, 26 were excluded (7 were aged less than 5 years; 13 had coingestion; 6 presented after 24 hours of ingestion) giving a net sample size of 52.

**Quantitative variables:** Ingested dose of Acetaminophen measured in Gram, International Normalized Ratio (INR), duration of hospital stay measured in days.

**Statistical methods:** Statistical analysis was done using IBM SPSS version 23.0 (SPSS Inc., Chicago, USA). All categorical variables are represented as percentages and continuous variables are represented as mean ± standard deviation (SD). Pearson correlation coefficient (r) was used to test the statistical significance of association of categorical variables. A p-value of $<0.05$ was considered as statistically significant.

**Data sources/measurement**: INR value is measured in DT 100, AST and ALT values are measured in COBAS 8000.

## Results

### *Participants*

*Study Population:* Patients within an age of 15-45 yrs who presented to Emergency Medicine with Acetaminophen within 24 hrs of ingestion. Out of the 78 subjects, 26 were excluded (7 were aged less than 5 years; 13 had co-ingestion; 6 presented after 24 hours of ingestion) giving a net sample size of 52.

### *Descriptive data*

Out of the 78 subjects, 26 were excluded (7 were aged less than 5 years; 13 had co-ingestion; 6 presented after 24 hours of ingestion) giving a net sample size of 52 patients who deliberately ingested acetaminophen, with 13 males (25%) and 39 females (75%), mean age of presentation was 23.67 ± 6.9 years. History of previous psychiatric illness was noted in 23.1% patients. None of the patients had other comorbidities. Gastric lavage and activated charcoal was done in 36 (69.2%) and 13 (25%) patients respectively. It was observed that none of the patients required liver transplant or expired.

Ingested amount of Acetaminophen had statistically significant correlation with initial INR with a p-value of 0.004. It was also noticed that the initial INR value and duration of hospital stay had a statistically significant correlation with P value of $<0.001$. Ingested dose of Acetaminophen had no correlation with first 24 hour AST and ALT value.

## Outcome data


**Fig 1:** Pie diagram showing percentage of gender distribution

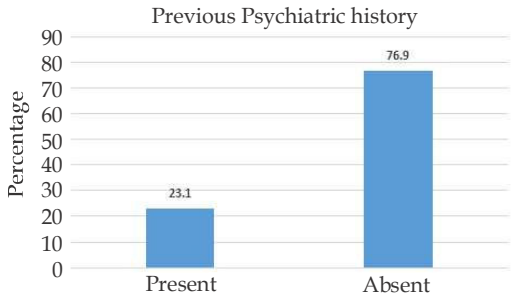



**Fig 2:** Bar diagram showing percentage of patients who had previous history of psychiatric illness

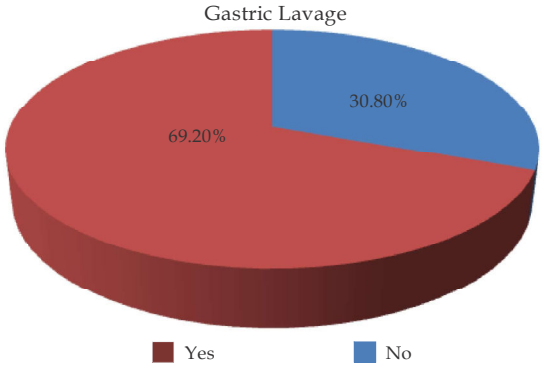



**Fig 3:** Pie chart showing the percentage of patients who underwent gastric lavage

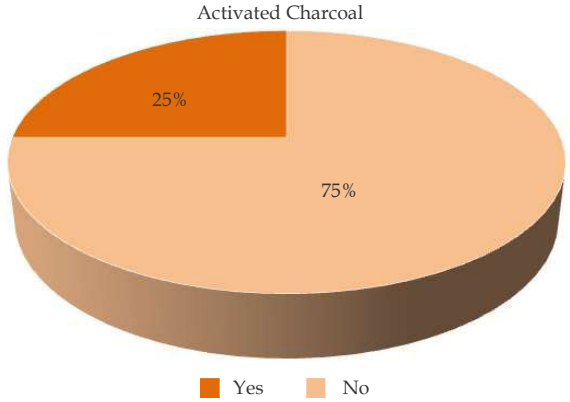
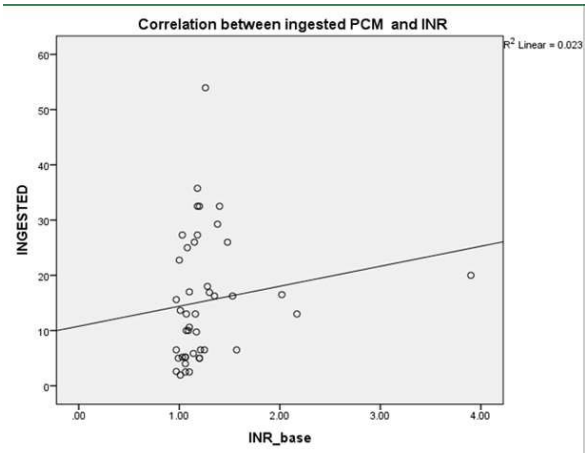



Fig 4: Pie chart showing the percentage of patients who underwent activated charcoal

**Table 1:** Correlation between ingested Acetaminophen level and International Normalized Ratio. The two variables Ingested Acetaminophen and International Normalized Ratio shows positive correlation and it is statistically significant

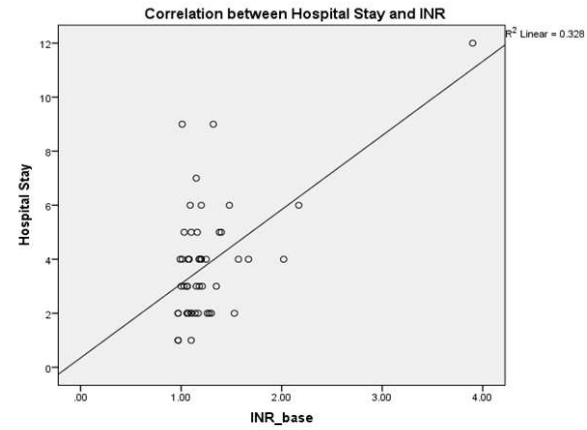
| Variable Name | n | Ingested Acetaminophen<br>Pearson correlation coefficient | p value |
|---|---|---|---|
| International Normalized Ratio | | +0.422 | 0.004 |




**Graph 1:** Correlation between International Normalized Ratio and Ingested dose of Acetaminophen

**Table 2:** Correlation between INR and duration of hospital stay. The two variables International Normalized Ratio and hospital stay shows positive correlation and it is statistically significant

| Variable Name | n | International Normalized Ratio<br>Pearson correlation coefficient | p value |
|---|---|---|---|
| Length of Hospital stay | | +0.573 | <0.001 |




**Graph 2:** Correlation between INR and duration of hospital stay

## Main results

## Other analysis

## Discussion

***Key results***

In the present study the correlation between the ingested acetaminophen dose and first 24 hour INR, AST, ALT was studied and was found that the initial INR correlated with the Acetaminophen ingested. And the initial INR correlated with the duration of hospital stay. There is no correlation between the ingested Acetaminophen dose with AST, ALT in this study. Therefore the first 24 hour INR can be used as a predictor of duration of hospital stay in Acetaminophen overdose.

**Table 3:** Correlation of ingested acetaminophen with ALT, AST, INR

| Variable name | Ingested acetaminophen Pearson correlation coefficient | p value |
|---|---|---|
| INR | .422 | .004 |
| ALT | .146 | .316 |
| AST | .084 | .570 |

***Limitations:*** The major limitation was that the study was conducted in a single centre. We would recommend a multicentre study with a larger number of recorders and interpreters for further validation. The initial Acetaminophen levels, effect of gastric lavage and activated charcoal on patient outcome, time of initiation of treatment are not discussed in this study.

## Other information

*Conflicts of interest*: None

Funding and other support: Nil

## Research Quality and Ethics Statement

The authors of this manuscript declare that this scientific work complies with reporting quality, formatting and reproducibility guidelines set forth by the EQUATOR Network. The authors also attest that this clinical investigation was determined to require the Institutional Review Board/ Ethics Committee review, and the corresponding protocol/approval number is [IRB-AIMS-2019-911]. We also certify that we have not plagiarized the contents in this submission and have done a Plagiarism Check.

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