

Clinical and Demographic Profiles of Children Presenting with Acetaminophen Induced Acute Liver Failure in a Tertiary Paediatric Intensive Care Unit of South India

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ABSTRACT

Introduction: Acetaminophen (APAP) is the most widely used over-the-counter antipyretic and analgesic medicine in children. Although hepatic failure and death is rare in paediatric population, it is one of the most important and dangerous presentation of acetaminophen induced toxicity in children. There is very sparse data regarding APAP induced paediatric acute liver failure in our settings, hence this study was done to know the clinical and demographic profiles as well as outcome of children with APAP induced acute liver failure.

Methods: This was a retrospective study done in children aged 0 - 18 years admitted with the diagnosis of acetaminophen induced acute liver failure in a tertiary paediatric intensive care unit of South India from January 2014 to December 2018. The clinical, demographic profiles and outcome of these patients were reviewed and analysed.

Results: A total of 26 children had acetaminophen induced acute liver failure. Out of 26 patients, 53.8% were males and 46.1% were females. Among these, 24 (92.3%) survived and two (7.7%) died. The average dose of acetaminophen ingested was 168.5 mg/kg/d. The mean serum acetaminophen level was 52.3 mg/dl. The presence of low pH, hypotension and international normalised ratio (INR) value of > 4 showed bad outcome in children with acetaminophen induced acute liver failure.

Conclusion: Paracetamol induced acute liver failure is rare but fatal presentation in children. Children with acidosis, shock and INR value of > 4 had poor prognosis. Hence, judicious use of different preparations as well as counselling to parents regarding use of appropriate doses in children should be done while prescribing this medicine.

Key words: Acetaminophen (APAP); Acute Liver Failure (ALF); Paracetamol



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INTRODUCTION

Acetaminophen, also known as N-acetyl-para-aminophenol (APAP) or paracetamol, is one of the most common over-the-counter medicine used in children. The safety and efficacy of acetaminophen is well proven in children as compared to aspirin. The recommended dose of paracetamol in children is 10 - 15 mg/kg every four to six hours up to a maximum daily dose of 50 - 75 mg/kg.¹ In general, the risk of developing adverse effects to paracetamol is lower in children as compared to adults.^{2,3} Though toxic effects of paracetamol are rare in children, its toxicity remains a concern due to wide range of usage of this drug.⁴ Previous reports have suggested that 120 - 150 mg/kg of body weight may be associated with hepatotoxicity.⁵⁻⁸ There are cases of liver injury, liver failure and deaths reported in children due to paracetamol toxicity. The majority of the severe cases are due to overdose. However, there are some case reports and case series which have reported deaths that may occur even with therapeutic dosing.⁹ Acute liver failure and death are uncommon outcomes of paracetamol toxicity.^{10,11} But it remains the most important cause of acute fulminant hepatic failure in Western countries.¹²

APAP induced hepatotoxicity is due to formation of N-acetyl-p benzoquinoneimine (NAPQI) metabolite. The presence of NAPQI in excessive quantities leads to depletion of adenosine triphosphate (ATP) stores and is augmented by the features of glutathione (GSH) depletion, oxidative stress and mitochondrial dysfunction.¹³⁻¹⁵ Other mechanisms of hepatotoxicity are the formation of toxic free radicals like peroxy nitrite from the reaction of superoxide and nitric oxide, then forming nitrotyrosine adducts inside the mitochondria.^{14,15} The hepatotoxic potential of multiple supratherapeutic doses of APAP is also important factor especially in critically ill children.^{16,17} These children may have reduced detoxification potential due to complications related to their illness and or treatment.¹⁸ The dosing threshold at which hepatic injury occurs after supratherapeutic paracetamol ingestion appears to be subject to wide inter-individual variation and depends on the dosing context.¹⁰

There is sparse data regarding APAP induced acute liver failure in children in Indian settings. The reason could be that ALF being an uncommon feature of paracetamol toxicity. Previous study¹⁹ has mentioned that exposure to multiple supra-therapeutic doses of paracetamol is a risk factor for developing fulminant hepatic failure in children. But, the exact dose of APAP at which hepatotoxicity occurs is still not known. Hence, this study was done to understand the clinical and demographic profiles of patients as well as to determine the outcome of children with APAP induced ALF admitted in tertiary care paediatric intensive care unit (PICU) in South India.

METHODS

This was a retrospective observational study done at PICU of Kanchi Kamakoti CHILDS Trust Hospital, Chennai, India. All the children aged between one month to 18 years admitted with diagnosis of APAP induced ALF were included in the study. APAP induced ALF was diagnosed when child had ingested acetaminophen more than the recommended dose i.e. > 75 mg/kg/day¹ with features of acute liver failure (ALF) defined by paediatric acute liver failure (PALF) group.²⁰ Neonates and children with chronic liver disease or failure were excluded. This study was done from January 2014 to December 2018. The data was collected from PICU database and hospital medical records. All the medical records of patients were reviewed. Data regarding demographic profile, clinical features, investigations, treatment and outcome were collected. The Kings College Hospital Criteria²¹ for predicting outcomes for acetaminophen induced liver failure was noted for all the patients. The qualitative data were analysed with Pearson's chi-square test and quantitative data were analysed using the student t-test. The data were analysed using SPSS 21.0 software.

RESULTS

Total of 115 children were admitted with paediatric ALF during this period and among this 26 were APAP induced ALF. Out of 26, 14 (54%) were males and 12 (46%) were females, making male : female ratio was 1.16. The minimum and maximum age of the children were five months and 72 months respectively with mean age of 21 months. The

Table 1. Clinical features of children with acetaminophen induced acute liver failure

Clinical Features	N (%)
Hepatomegaly	23 (88.5)
Hepatic Encephalopathy (HE)	22 (85.0)
• Grade 1-2	16 (72.7)
• Grade 3-4	6 (27.3)
Edema	11 (42.3)
Ascites	11 (42.3)
Bleeding	10 (38.5)
• Minor	8 (80.0)
• Major	2 (20.0)
Jaundice	4 (15.4)
Multi-organ dysfunction syndrome (MODS)	4 (15.4)

mean weight of children was 10.2 kg (range 6.5 - 20 kg). In all the children of APAP induced ALF, the cause was due to unintentional use of APAP and all were less than seven years of age. Out of 26, most of the patients had hepatomegaly (88.5%) and signs of hepatic encephalopathy (85%). The rest of the clinical features are stated in Table 1.

The mean length of stay in PICU was 4.3 days (range 1 - 15 days). Of total 26 children, 24 (92.3%) survived and two (7.7%) died. Out of 26 children, 12 (46.1%) met and 14 (53.8%) did not meet King's college hospital criteria (KCHC) for predicting outcomes in patient with acetaminophen induced ALF. All the children with acetaminophen induced ALF had exposure to supra-therapeutic doses of acetaminophen i.e. > 75 mg/kg/day. The range of acetaminophen dose ingested by children above the recommended dose is shown in Table 2. The mean, minimum and maximum values of laboratory findings of patients with APAP induced ALF are shown in Table 3.

Out of 26 children, 12 (46%) required invasive mechanical ventilation and six (23%) needed inotropes. The average duration of mechanical ventilation days was 3.3 days. Seven (26.9%) children required haemodialysis for acute kidney injury. Nineteen (73%) children required fresh frozen plasma for bleeding. All children were started on N-acetyl cysteine. None underwent liver

Table 2. The range of acetaminophen dose (mg/kg/day) ingested by children with acetaminophen induced acute liver failure

Acetaminophen dose (mg/kg/day)	N (%)
< 75	0 (0.0)
75 - 100	5 (19.2)
101 - 125	2 (7.7)
126 - 150	6 (23)
151 - 175	4 (15.4)
176 - 200	2 (7.7)
> 200	7 (26.9)

transplantation. In univariate analysis, hepatic encephalopathy ($p = 0.53$), bleeding ($p = 0.06$),

Table 3. Laboratory investigations in children with acetaminophen induced acute liver failure

Variables	Minimum	Maximum	Mean
Acetaminophen dose (mg/kg/d)	80	300	168.5
Serum acetaminophen level (mg/dl)	7	85	52.3
Alanine transaminase (ALT) (IU/L)	1130	16328	6622.3
Aspartate transaminase (AST) (IU/L)	1120	28929	8428.88
Total serum bilirubin (mg/dl)	0.3	2.6	1.53
Direct bilirubin (mg/dl)	0.2	1.8	0.99
Albumin (mg/dl)	2.1	4.1	2.87
Ammonia (micro/dl)	29	392	142.08
Lactate (mmol/L)	2	12.7	5.46
Creatinine (mg/dl)	0.12	4.46	1.14
pH	7.1	7.44	7.28
Prothrombin time (seconds)	21.3	105	52
International normalized ratio (INR)	1.8	10.3	4.3
Activated partial thromboplastin time (seconds)	30.7	> 2 minutes	46.3

multi-organ dysfunction syndrome ($p = 0.16$) and INR value of > 4 ($p = 0.2$) were not statistically significant for predicting outcomes. Only those children who required inotropes were associated with poor outcomes ($p = 0.007$). Similarly, for laboratory parameters total serum bilirubin ($p = 0.55$), alanine transaminase ($p = 0.29$), aspartate aminotransferase (0.53), peak ammonia ($p = 0.82$), minimum serum albumin ($p = 0.35$), peak lactate ($p = 0.57$) and maximum creatinine ($p = 0.13$) were not found to be statistically significant for predicting outcomes in children with APAP induced ALF. However, child with acidosis was associated with poor outcome ($p = 0.039$).

DISCUSSION

APAP induced ALF though rare is one of the dangerous presentation of APAP toxicity. This study was done to determine clinico-demographic profile and outcome of children with APAP induced ALF. In our study APAP induced ALF was most common in males and most of them survived. The most common features were hepatomegaly and HE and all had exposure to supra-therapeutic dose of APAP. The exact dose of APAP at which hepatotoxicity occurred was not known. Previous study by Rumack and Matthew emphasised that there is prolongation of the half-life of APAP from liver toxicity but did not indicate a minimum dose for toxicity.²² APAP is considered as a hepatotoxin which leads to liver damage. The biochemical signs of hepatic injury may occur 24 hours after the APAP overdose that leads to dose-related centrilobular hepatic necrosis.²³⁻²⁵

In our study PALF was attributed by APAP toxicity in 26 out of 115 (22.6%) which was similar to the study by Rajanayagam J et al. which reported 14 out of 54 (25.9%).²⁶ Our study showed male preponderance of 54% in APAP induced ALF which was in contrast to the study by J Rajanayagam et al.²⁶ (64.3%) and Sarah W et al.²⁷ (74%) which showed female preponderance. In our study, 100% of APAP induced ALF were unintentional which was in contrast to the study by Sarah W et al.²⁷ which reported majority of patients with intentional ingestion (92.6%) and only 3.7% of unintentional ingestion of APAP in children. The reason may be APAP being one of the most

common intentional drug overdoses in western countries. Study by Sarah W. et al reported that hepatocellular injury was more prevalent in 10-17 years children (96.3%).²⁷ This was in contrast to our study as all the children with acetaminophen induced hepatotoxicity were under seven years of age. This difference may be due to exposure to supra-therapeutic dose of paracetamol to immature liver in young children in our settings and intentional use of paracetamol by adolescent age groups in western countries.

Study by Rajanayagam J et al. reported HE in nine out of 54 (16.7%) patients which was in contrast to our study where HE was found in 22 (85%) of patients.²⁶ In our study, 61% had HE grade I-II and 23% had grade III-IV which was in contrast to the study by Sri Ranganathan et al. who reported HE grade I-II in 96% of patients and HE grade III in 4% of patients.¹⁹ In our study hepatomegaly was present in 23 (88.5%), jaundice in four (15.4%) and renal failure in four (15.4%) patients which was higher as compared to the study by Sri Ranganathan et al. where hepatomegaly, jaundice and renal failure were reported in 21 (84%), 4 (16%) and 2 (8%) patients respectively.¹⁹ Study by Sri Ranganathan et al.¹⁹ reported 12% of deaths in children due to APAP liver toxicity which was more compared to our study where 7.7% of patients died due to APAP induced ALF. The reason for this may be due to the severity of illness at presentation.

In our study the dose range of APAP ingested causing ALF was 80 – 300 mg/kg/d which was slightly higher than the reported value by J. Rajanayagam et al.²⁶ where APAP dose ranges from 62 - 250 mg/kg/d. The mean daily APAP ingested dose in our study was 168.5 mg/kg/d which was higher compared to the study by Sri Ranganathan et al. who reported the average dose of APAP ingestion to be 145 mg/kg/d.¹⁹ In the Study by Sri Ranganathan et al.¹⁹ the mean alanine aminotransferase was 2781 IU/L which was less compared to our study where it was 6622.23 IU/L. The reason for this may be due to the high grade of hepatic injury in our cohort of patients. In our study, all patients received N-Acetyl cysteine for APAP toxicity whereas in the study by Sri Ranganathan et al., only 68% of cases received

N-Acetyl-cysteine and other patients were managed symptomatically.¹⁹ Study by Rajanayagam J et al. reported liver transplantation in three patients whereas in our study none of the patients underwent transplantation. The reason for this may be due to non availability of organ donors as well as parents' financial constraints.²⁶

The limitations of this study are that this study is retrospective and has a small sample size, based upon a single centre. Hence, further prospective studies should be done to determine the clinico-demographic profiles and risk factors for predicting the outcome of children with APAP induced ALF.

CONCLUSIONS

Acetaminophen induced acute liver failure is one of the rare but dangerous complications of acetaminophen toxicity. The ingestion of acetaminophen beyond therapeutic doses can cause liver toxicity but the exact dose at which acetaminophen induced acute liver failure occurs is not known. Hence, we need to be cautious and familiar with locally available preparations and doses while prescribing paracetamol for children.

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