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Research Article

EVALUATION OF THE ADVERSE OUTCOMES OF PARACETAMOL IN HOSPITALIZED PAEDIATRIC PATIENTS: A SINGLE CENTRE STUDY

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ABSTRACT

Objective: Paracetamol is one of the effective and well-tolerated drugs by pediatrics and adults in therapeutic doses. The purpose of this study was to examine whether therapeutic doses of acetaminophen are associated with adverse outcomes in hospitalized pediatrics patients.

Methods: Thirty children of both sexes aged 6-14 years were enrolled in a single-center, parallel-group study design. Therapeutic doses according to the body weight of neonates and children can be administered in hospital settings. The statistical analysis was performed using SPSS software (version 17.0).

Results: This study showed mean±standard deviation (SD) of age in cases and controls were observed to be 8.47±2.980 and 8.75±2.849, where the p=0.66 which is statistically not significant. The body mass index was observed to be 12.40±3.179 and 10.33±2.267 are statistically significant. The mean±SD of cases and controls were found to be 29.10±13.42 and 27.10±8.17. There is a slight increase in the mean serum glutamic oxaloacetic transaminase levels in cases when compared to control groups. The mean serum glutamic-pyruvic transaminase levels slight increases in cases, when compared to control groups were 26.18±48.94 and 24.36±5.92.

Conclusion: These findings conclude that, paracetamol is not causing hepatotoxicity, hematological, and nephrotoxicity. Even in supratherapeutic dosing in 25% of the study population we did not find any adverse effects, whose therapeutic level is above 20 µg/ml up to 30 µg/ml. Though standard, recommended therapeutic doses of paracetamol were prescribed in all study population 25% of children showed supratherapeutic levels, which did not show clinical or biochemical signs of toxicity.

Keywords: Therapeutic levels, SPSS, Pediatrics, Age, Toxicity.

INTRODUCTION

Paracetamol (acetaminophen, 4 hydroxyacetanilide, N-acetyl-para-aminophenol, 4 acetamidophenol) is the most popular analgesic in most countries in the world. In normal doses, it is remarkably free from adverse effects and interactions with other drugs, even in patients with established liver disease [1]. Its use has been further stimulated by the perceived risks of the other previously popular over-the-counter analgesic aspirin, notably its gastrointestinal effects, and its association with Reyes syndrome in children. The easy availability of paracetamol in shops and pharmacies without prescription has led to it being kept in many homes and it is, therefore, not surprising that it is often involved in episodes of accidental or deliberate self-poisoning. Between 1968 and 1973, annual hospital admissions for paracetamol overdosage increased from 150 to 7000 in the United Kingdom [2] and in 1989 the drug was involved in 29% of admissions with poisoning in one district hospital in Wales [3] and in 13% in a London hospital between 1984 and 1988. The age and sex distribution of paracetamol poisoning matches that of other drugs taken in overdose [4] and the peak age group involved is between 20 and 30 years [5]. In a survey of patients taking drug overdoses in New-castle upon Tyne, paracetamol was taken by 41% of those under 35 years, but by only 11% of those over 65 years who are more likely to take drugs prescribed for them or for their spouses [6]. Therefore, the present aim of the study to investigate on adverse effects of paracetamol Hepatotoxicity, Renal toxicity, and Hematological toxicity) in Pediatrics patients receiving drugs due to febrile illness in MGM hospital, Warangal by estimating laboratory findings.

METHODS

Study design

Study design is a case-control study approved by the ethical committee and informed consent from parents of each patient were taken.

Cases

Totally, 30 children (N=30) of inpatients in Department of Pediatrics, MGM, Hospital, Kakatiya Medical College, Warangal, Telangana, India admitted with febrile illness prescribed with paracetamol as per clinical indication by treating doctors between March 2012 and October 2012 with their demographic data (Age, Sex, body mass index [BMI]) were recruited as cases.

Controls

Healthy afebrile children belonging to the same population as that of cases and of similar age and sex from government primary and secondary school Kazipet, Warangal, Telangana, India were recruited as controls after informed consent is taken from parents and permission from the school authorities was taken.

Experimental protocol

Blood samples were obtained from cases in the hospital after explaining the parents regarding the use and procedure of the study. Experiments using a collection of 5 ml of blood sample who are receiving paracetamol after repeated therapeutic doses at a half-life period of 4 hrs. Blood samples were obtained from an antecubital vein. Blood samples of control groups were drawn in the school in the presence of teachers by a trained lab technician. Serum was separated from the collected 5 ml blood samples within 2 hrs and were stored at −20°C till biochemical

analysis. The physical examination included measurements of blood pressure and BMI. Blood pressure was measured using a standard mercury manometer. BMI was calculated by dividing the subject's weight (measured in kilograms with the subject barefoot).

MATERIALS

Reagents and chemicals

Sodium nitrite ($NaNO_2$, MW 69.0), Sodium hydroxide, sulfamic acid, and trichloroacetic acid were procured from Qualigens fine chemicals, Mumbai. Reference standards of paracetamol were procured from Unichem pharmaceuticals, Mumbai.

Estimating parameters

1. Liver function tests: Serum glutamic oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT), and total bilirubin were estimated using the kits (Coral Clinical systems; Ensure Biotech Ltd) with colorimetric methodology.
2. Kidney function tests: Serum creatinine and blood urea were estimated using the kits (Excel diagnostics ltd) with UV-visible spectrophotometer Elico SL 164.
3. Complete blood count: The Coulter HMX Hematology Analyzer is a quantitative, automated hematology analyzers, and leukocyte differential cell counters for *in vitro* diagnostic use in clinical laboratories. These studies include further measurements of cell size and cell distribution, biochemical investigation or any other test that helps diagnose the abnormality. Here we observe biochemical investigation of hemoglobin (Hb), mean corpuscular volume, platelets, etc.,
4. Estimation of paracetamol: Paracetamol powder was used to prepare 1 mg/ml stock solution that was prepared by dissolving the powder in warm distilled water. The stock solution was used to prepare 8 series of (100 µg/ml) working standards 5, 10, 20, 30, 40, 50, 60, 100 µg/ml. It was based on the Glynn and Kendal method with a few modifications to the volume of sample and reagents to decrease the production of nitrous gas. In the modified method, 0.5 ml of plasma was pipetted into a 15 ml centrifuge tube containing 1.0 mL of 15% trichloroacetic acid. After vortex mixing, it was centrifuged briefly for 3 minutes and the clear supernatant were decanted into a 10 ml test tube containing 0.5 ml 6 N hydrochloric acid. Nitrous acid was generated by adding 0.4 ml of sodium nitrite to the resulted solution. After allowing the contents to stand for 2 minutes 1.0 ml of 15% sulfamic acid was added carefully to neutralize the excess nitrous acid. Finally, 2.5 ml 15% sodium hydroxide was added and the absorbance of each sample was measured at 430 nm, against a reagent blank of water [7].

Therapeutic level of paracetamol is 10-20 µg/ml.

Statistical analysis

The results are prescribed as mean±standard deviation (SD) 5 to 6 independent experiments. Comparison where made using the independent t-test for equality of variances (Sig 2-tailed) between variables, respectively, (SPSS 17.0). The level of significance was considered to be $p \leq 0.05$.

RESULTS

Overall study population

Eighty-six children recruited based on inclusion criteria and divided into two groups of paracetamol administered (n=30) and controls (n=56). The patients' baseline characteristics were comparable across the group (Table 1) there were no significant differences in gender population.

None of the patients in both study groups had dyspnea, skin rash, anaphylactic shock, and thrombocytopenia during our study population. There were no deaths in either group. When compared to normal subjects of our study population reduced body weight group in febrile patients 19.47±5.051 kg.

The between occasion variability for case vs. control groups. The change in biochemical parameters of study group, significantly slightly increased serum bilirubin, SGOT, SGPT, Creatinine, and blood urea nitrogen (BUN) levels. When compare to control subjects (Table 2).

Comparison of cases and controls in different parameters shown in Figs. 1-8.

Baseline characteristics

Age

The mean±SD of age in cases and controls were observed to be 8.47±2.980 and 8.75±2.849 years; where p=0.66, which is statistically not significant.

Table 1: Gender distribution of our study subjects

Gender	Case	Control	Total	Percentage
Female	12	27	39	45.3
Male	18	29	47	54.65
Total	30	56	86	

Table 2: Group statistics (cases versus controls)

Patients characteristics	Group	N	Mean	SD	Standard error mean
Age	Control	56	8.75	2.849	0.381
	Case	30	8.47	2.980	0.544
Height	Control	56	141.32	13.645	1.823
	Case	30	124.23	17.459	3.188
Weight	Control	56	20.96	6.120	0.818
	Case	30	19.47	5.051	0.922
BMI	Control	56	10.33	2.267	0.303
	Case	30	12.40	3.179	0.580
SGOT	Control	56	27.958929	8.1725656	1.0921050
	Case	30	29.950000	13.4288868	2.4517681
SGPT	Control	56	24.366	5.9234	0.7915
	Case	30	26.183	48.9406	8.9353
Bilirubin	Control	56	0.744821	0.1767072	0.0236135
	Case	30	0.750333	0.4428784	0.0808582
BUN	Control	56	30.014107	9.1545972	1.2233345
	Case	30	30.630000	15.7563023	2.8766941
Creatinine	Control	56	0.820536	0.2114231	0.0282526
	Case	30	0.753800	0.2896572	0.0528839
Hb	Control	56	10.567857	0.6229277	0.0832422
	Case	30	9.803333	1.5663450	0.2859742
WBC	Control	56	9809.29	1298.547	173.526
	Case	30	8420.00	4747.006	866.681
RBC	Control	56	323035.71	67066.308	8962.112
	Case	30	345333.33	105625.667	19284.520
Platelet	Control	56	255125.00	60430.294	8075.338
	Case	30	228000.00	71871.533	13121.887

SD: Standard deviation, BMI: Body mass index, SGOT: Serum glutamic oxaloacetic transaminase, SGPT: Serum glutamic-pyruvic transaminase, BUN: Blood urea nitrogen, Hb: Hemoglobin, WBC: White blood cell, RBC: Red blood cell

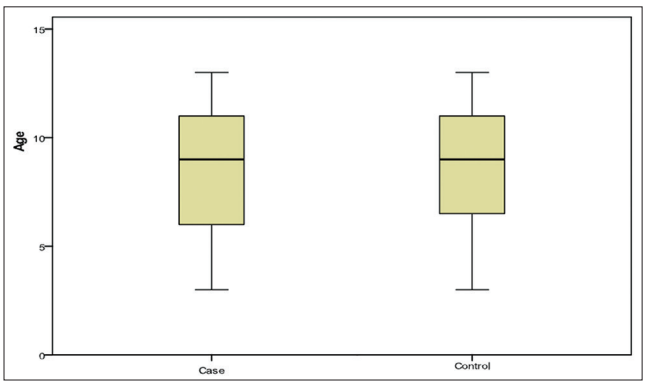

Fig. 1: Age distribution in cases and controls

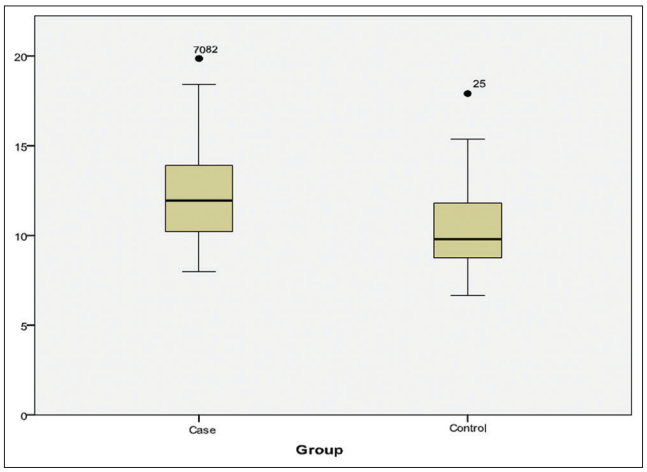

Fig. 2: Body mass index (BMI) distribution in cases and controls with two standard deviations. In the above graph 70, 82, 25 are the serial numbers of the data entered in the software bearing a unique ID number SP21, SP5, C31 are having higher BMI than normal

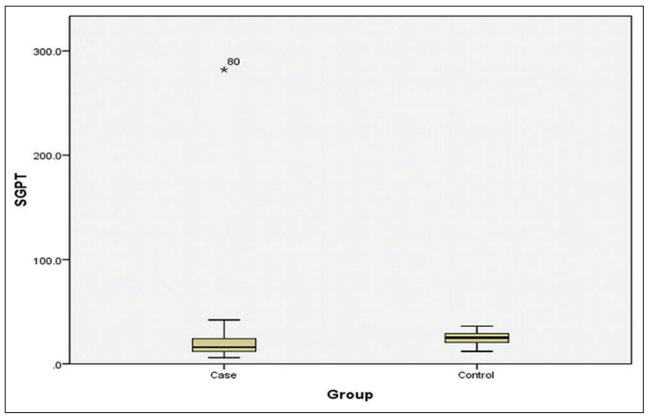

Fig. 3: Serum glutamic-pyruvic transaminase (SGPT) levels in cases and controls with two standard deviations. In the above graph, 80 is serial number of data entered in the software whose ID is SP30 having higher SGPT levels

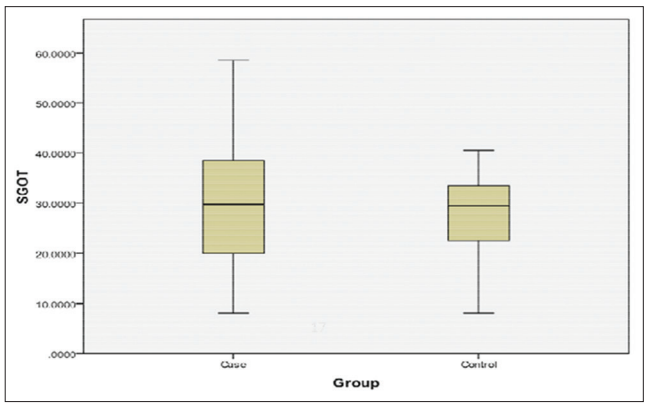

Fig. 4: Serum glutamic oxaloacetic transaminase levels in cases and controls with two standard deviations and mean values

Height

The mean±SD of height in cases and controls were observed to be 124.23±17.459 and 141.32±13.645 cm; where p=0.001, which is statistically significant.

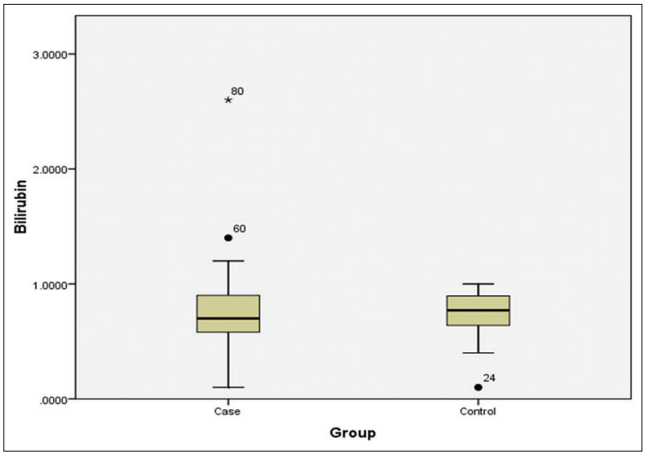

Fig. 5: Bilirubin levels in cases and controls with two standard deviations and mean values. In the above graph 80, 60, and 24 are the serial numbers of data entered in the software whose UID is SP30, S12, and C33 showing abnormality in serum glutamic oxaloacetic transaminase levels

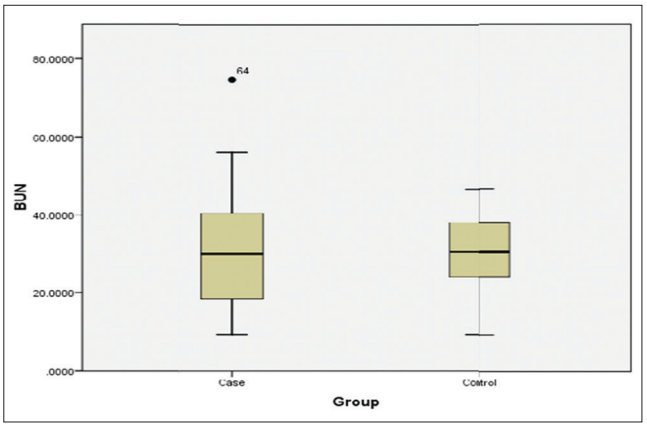

Fig. 6: Blood urea nitrogen values in cases and controls with two standard deviations and mean values. In the above graph, 64 is the serial number of data entered in the software bearing a UID SP16 whose blood urea nitrogen value is exceeding above the normal range

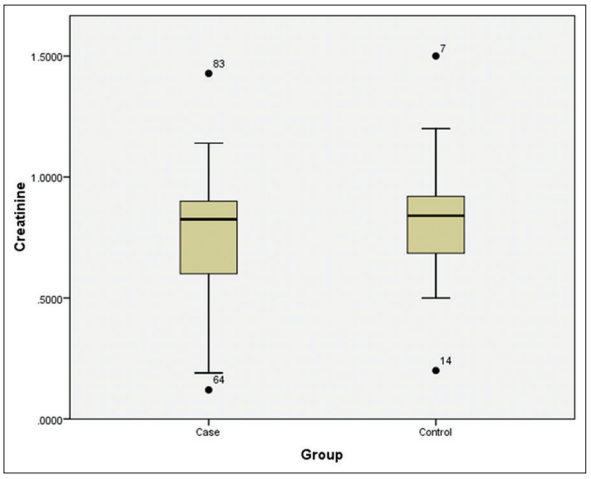

Fig. 7: Serum creatinine levels in cases and controls with standard deviations and mean values. In the above graph 83, 64, 14, and 7 are the serial numbers of data entered in the software with UID of SP6, SP8, C15, and C21

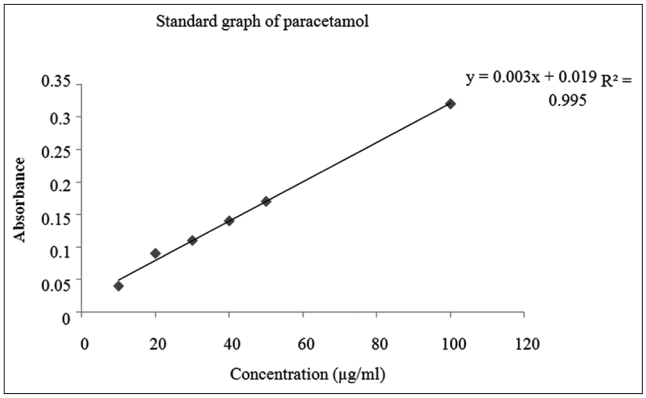

Fig. 8: Standard graph of paracetamol with slope and regression

Weight

The mean±SD of weight in cases and controls were observed to be 19.47±5.051and 20.96**±**20.96 kg; where p=0.255, which is statistically not significant.

BMI

The mean±SD of BMI in cases and controls were observed to be 12.40±3.179 and 10.33±2.267 kg/m;^{2} where p=0.001, which is statistically significant.

Aspartate transaminase (AST)

There were statistically no significant difference (p=0.462) in the plasma activities of SGOT in cases treated with paracetamol as compared to control groups. The mean±SD of cases and controls were found to be 29.10±13.42 and 27.10±8.17 U/L. There is a slight increase in the mean SGOT levels in cases when compared to control groups.

Alanine transaminase (ALT)

There were statistically no significant difference (p=0.84) in the plasma activities of SGPT in cases as compared to control groups. The mean±SD of cases and controls were found to be 26.18±48.94 and 24.36±5.92 U/L. There is a slight increase in the Mean SGPT levels in cases when compared to control groups.

Bilirubin

There were statistically no significant difference (p=0.948) in the plasma activities of Bilirubin in cases as compared to control groups. The mean±SD of cases and controls were found to be 0.75±0.44 and 0.74±0.17 mg/dL. There is a slight increase in the mean bilirubin levels in cases when compared to control groups.

BUN

There were statistically no significant difference (p=0.845) in the serum activities of BUN in cases treated as compared to control groups. The mean±SD of cases and controls were found to be 30.63±15.75 and 30.01±9.15 mmol/L. There is a slight increase in the mean bilirubin levels in cases when compared to control groups.

Serum creatinine

There were statistically no significant difference (p=0.052) in the serum activities of serum creatinine in cases as compared to control groups. The mean±SD of cases and controls were found to be 0.75±0.28 and 0.82±0.21 g/dL. There is a slight increase in the mean bilirubin levels in cases when compared to control groups.

Hematological parameters

Hb

There were statistically a significant decrease in Hb of cases when compare to controls (p=0.015). The mean±SD of Hemoglobin in cases and controls were found to be 9.8±1.5 and 10.5±0.62 (g/dL).

White blood cells (WBC)

There were statistically a slight decrease in WBC of cases when compare to controls (p=0.04). The mean±SD of WBC in cases and controls were found to be 8420±4747; 9809±1298 (1000 cells/uL).

Red blood cells (RBC)

There is no significant effect in RBC of cases when compare to controls (p=0.2). The mean±SD of RBC in cases and controls were found to be 345333±19284; 32305±67066 (million cells/uL).

Platelet count

There is no statistically significant in platelet count of cases when compare to controls (p=0.06). However, the mean±SD of platelets are decreased in cases when compared to controls whose values are found to be 228000±71871; 255125±60430 (1000 cells/uL).

DISCUSSION

In the present study, BMI of cases is significantly more than controls. The mean±SD of BMI in cases are 12.04±3.17 and controls are 10.33±2.26. In 25% of cases (6 out of 30) in our study paracetamol levels are exceeding the therapeutic range (>20 µg/ml). One possible reason could be relatively low BMI in them. A study (Zenger *et al*., 2001) reveals that low BMI patients exhibit a deficiency of glutathione levels, where NAPQI accumulation is increased which leads to a supratherapeutic level of paracetamol. In our study though 25% of cases are having supratherapeutic paracetamol levels (>20 µg/ml), none of them showed an abnormal values of ALT, AST, and bilirubin levels. As per Penna *et al*., 1991 study children are less prone to paracetamol hepatotoxicity because of developmental differences in the drug metabolism and its pathways of detoxification [8]. Although children appear to tolerate single, high-dose ingestion well (up to 50 µg/ml), the studies are replete with reports of significant morbidity and mortality after repeated supratherapeutic dosing. Risk factors for injury with chronic use include age, total dose, duration, the presence of intercurrent febrile illness, Starvation [9]. In our study, there is no significant difference in the ALT of cases when compared to controls. The mean±SD of ALT in cases is 26.18±48.94 and controls is 24.36±5.92; p=0.8. In 2 cases, the ALT levels are elevated (>35 IU/dL) but their plasma paracetamol levels are within the therapeutic range (10-20 µg/ml) the raised levels may be due to the disease process (Malaris and cholongitis). There is also no significant difference in AST of cases and controls, the mean±SD in cases are 29.95±13.42 and controls are 27.95±8.17; p=0.4, but in 6 cases AST levels are increased above the normal range (>40 IU/dL). The plasma paracetamol levels are normal in 5 of them and decreased in one patient, the reason for the above result may be due to individual metabolism or other co-morbidities. There is no significant difference in bilirubin in cases when compared to controls cases 0.75±0.44; controls: 0.74±0.17; p=0.9). Cases have significantly decreased Hb levels when compared to controls. The mean±SD of cases is 9.8±1.5 and controls are 10.56±0.62; p=0.01. As in both the groups the HB levels are low according to WHO, so there is no clear evidence to attribute it to paracetamol. There is also a significant decrease in WBC of cases when compared to controls (cases: 8420±4747; controls: 9809±1298; p=0.04) but in both groups the WBC values are within the normal range as per age. The relative decrease in WBC count in cases may be because of viral infections or other illness which causes suppression of WBC. The mean±SD of platelet in cases are 228000±71871 and controls are 255125±60430; p=0.06 which is statistically not significant. However, Thomas *et al.*, 1993 reported that severe thrombocytopenia and leucopenia is caused by paracetamol toxicity at a supratherapeutic level above 50 µg/ml. In the present study, there is no significant effect of paracetamol on hematological parameters (Hb, WBC, Platelets) even in patients with elevated plasma paracetamol concentration (>20-0 µg/ml). In our study, there is no significant effect of paracetamol on BUN and serum creatinine. The mean±SD of BUN in Cases are 30.63±15.75 and controls are 30.01±9.15; p=0.8 and the mean±SD of serum creatinine in cases is 0.75±0.28 and controls 0.82±0.21; p=0.2. Less frequently Thomas *et al*., 1966 described paracetamol-induced nephrotoxicity in 2% of cases with a plasma paracetamol concentration

of above 63 µg/ml, which shows that the frequency of paracetamol on renal failure is very less [10].

CONCLUSION

There are many options to clinicians to prescribe antipyretics. Concerns are raised regarding paracetamol safety, its dose and duration of therapy. The present study shows that paracetamol usage is not causing hepatotoxicity, hematological, and nephrotoxicity where paracetamol levels are increased from 21 to 30 µg/ml. Even in supratherapeutic dosing in 25% of the study population we did not find any side effects on liver, kidney, and hematological parameters whose therapeutic level is above 20 µg/ml up to 30 µg/ml. Though standard, recommended therapeutic doses of paracetamol were prescribed in all study population 25% of children showed supratherapeutic levels, which did not show clinical or biochemical signs of toxicity. However, reasons for supratherapeutic levels of paracetamol like excess use, co-morbidities, co- medication, and others should be probed by further investigations or studies. From the present study, we conclude that the Pediatric guidelines for the treatment of antipyretic and analgesic therapy with paracetamol is safe, and efficacious even up to a therapeutic level of 20-30 µg/ml.

REFERENCES

1. Benson GD. Acetaminophen in chronic liver disease. Clin Pharmac Ther 1983;33(1):95-101.
2. Volans GN. Self-poisoning and suicide due to paracetamol. J Int Med Res 1976;4(4):7-13.
3. Janes J, Routledge PA. Recent developments in the management of paracetamol (acetaminophen) poisoning. Drug Saf 1992;7(3):170-7.
4. Mitchell S. Relational Concepts in Psychoanalysis: An Intergration. Cambridge MA: Harvard University Press; 1988. p. 13-6.
5. Prescott LF. Paracetamol overdosage. Pharmacological considerations and clinical management. Drugs 1983;25(3):290-314.
6. Wynne H, Bateman DN, Hassanyeh F, Rawlins MD, Woodhouse KW. Age and self-poisoning: The epidemiology in Newcastle upon Tyne in the 1980s. Hum Toxicol 1987;6(6):511-5.
7. Glynn JP, Kendal SE. Letter: Paracetamol measurement. Lancet 1975;1(7916):1147-8.
8. Penna A, Buchanan N. Paracetamol poisoning in children and hepatotoxicity. Br J Clin Pharmacol 1991;32(2):143-9.
9. Sztajnkrycer MJ, Bond GR. Chronic acetaminophen overdosing in children: Risk assessment and management. Curr Opin Pediatr 2001;13(2):177-82.
10. Thomson JS, Prescott LF. Liver damage and impaired glucose tolerance after paracetamol overdosage. Br Med J 1966;2(5512):506-7.