https://doi.org/10.29309/TPMJ/2022.29.06.6103

The Professional Medical Journal
www.theprofesional.com
2022, Volume, 29 Issue, 06

ORIGINAL ARTICLE

Paracetamol induced liver enzyme (AST/ALT) changes in dengue fever.

Kiran Hafeez[1], Muhammad Akbar Memon[2], Zia Farooqui[3], Haseeb Jameel Memon[4], Kamran Baig Memon[5], Abdul Aziz[6]

Article Citation: Hafeez K, Memon MA, Farooqui Z, Memon HJ, Memon KB, Abdul Aziz. Paracetamol induced liver enzyme (AST/ALT) changes in dengue fever. Professional Med J 2022; 29(6):780-784. https://doi.org/10.29309/TPMJ/2022.29.06.6103

ABSTRACT… Objective: To determine the Paracetamol induced liver enzyme (AST/ALT) changes in dengue fever in a tertiary care hospital of Hyderabad. **Study Design:** Observational Study. **Setting:** Emergency Department of Medicine, Isra University Hospital, Hyderabad. **Period:** May 2018 to May 2019. **Material & Methods:** A total of 100 patients of age ≥12 years with dengue fever were included. AST and ALT levels were obtained in the first week and third week of course of illness. Paracetamol was used for anti-pyretic/analgesia purpose was compared of first week with third week. Statistical analysis was done using SPSS. Chi-square test and student's t-test were applied as appropriate. P value ≤0.05 was considered as significant. **Results:** Out of total 100 patients, there were 56% males and 44% females and overall mean age was 35.21±15.13 years. The overall mean weight, height, BMI, and mean duration of fever in days was 61.13±17.26 kg, 1.60±0.14 meter, 23.85±6.73 kg/m^2, and 4.20±1.43 days, respectively. Independent t test shows significant mean difference of AST/ALT ratio at 1st week (p=0.000) as well as at 3rd week (p=0.020) according to paracetamol dose. **Conclusion:** In our study, results showed significant improvement in AST, ALT, and AST/ALT ratio at 1st week and 3rd week.

Key words: Dengue Fever, Liver Damage, Pakistan.

INTRODUCTION

Family of a flavivirus called Dengue virus consisted of four serotypes is associated with three main clinical forms ranging from mild illness to severe one. These three types are commonly known as i) acute febrile illness which is associated with sudden onset of fever then followed by other symptoms of dengue such as arthralgia and skin rashes. These patients usually recover without any complication, ii) dengue hemorrhagic fever is also a type of acute dengue illness but it is associated with thrombocytopenia resulting in an increased vascular permeability leading to hemorrhage, and iii) the most severe form is dengue shock syndrome which is least common but these patients sudden develops life threatening hypotension resulting in high fatality rate ranging from 40% - 50% of the cases if left untreated.[1,2]

Derangements in liver functions are not so uncommon in patients affected with dengue fever and can be attributed by the presence of altered AST or ALT levels or either assessed by AST/ALT ratio. Besides laboratory parameters there are certain imaging modalities which may indicate liver injury such as Hepatomegaly in patients with dengue feve.[3,4] If these patients left untreated they may present with fulminant hepatic failure or sometimes with hepatic encephalopathy but cases to such extend are considerably low. Liver failure or liver injury caused by oral ingestion of tablet paracetamol is one of the most important causes cannot be neglected in patients diagnosed with dengue fever because the paracetamol is the most common drug and can be purchased over the counter and are used for the symptomatic relief of patients with dengue fever. The exact mechanism through which it causes liver injury is still not known or well established.[5-7]

Therapeutic doses of paracetamol may cause liver injury in some patients. Several authors[8-11] have found elevated levels of alanine transaminase

1. MBBS, FCPS (Medicine), Assistant Professor Medicine, Isra University Hospital. Hyderabad, Sindh, Pakistan.
2. MBBS, FCPS (Medicine), Associate Professor Medicine, Isra University Hospital Hyderabad, Sindh, Pakistan.
3. MBBS, MRCP, Senior Registrar Medicine, Isra University Hospital Hyderabad, Sindh, Pakistan.
4. MBBS, Resident, Civil Hospital, Hyderabad.
5. MBBS, MD (Internal Medicine) Senior Registrar Medicine, Isra University Hospital Hyderabad, Sindh, Pakistan.
6. MBBS, MRCP, Medical Welfare Ward, Isra University Hospital Hyderabad.

Correspondence Address:
Dr. Kiran Hafeez
Department of Medicine
Isra University Hospital,
Hyderabad, Sindh, Pakistan.
dr_kiranhafeez@yahoo.com

Article received on: 24/09/2020
Accepted for publication: 16/06/2021

(ALT) more than 3 times the upper limit of normal in 31 – 44% of persons receiving therapeutic doses of paracetamol (4g/day). Paracetamol metabolism is impaired in acute liver failure.

In this study, we want to compare different doses of paracetamol, used as an anti-pyretic and analgesic agent in patients with dengue fever, causing change in AST/ALT ratio.

MATERIAL & METHODS

This prospective observational study has been conducted in the Emergency Department of Medicine of a tertiary care Hospital, Isra University Hospital, Hyderabad, between the periods of nine months from 1st May 2018 to 28th May 2019. We have evaluated a total of 100 patients who were presented and admitted in the department of emergency/medicine with signs and symptoms of dengue fever, having age ≥ 12 years, duration of dengue fever less than one week of either gender. Patients with dengue hemorrhagic fever and dengue hemorrhagic shock syndrome were excluded from the study. This study has been conducted after the approval from the ethical review committee (IUH/E2018/33) of the hospital and after taking informed and written consent from the patients.

A 5cc disposable syringe was used for sample collection after following all aseptic measures such as NS1Ag, Dengue IgM or PCR and AST/ALT levels. Diagnosis of dengue fever was made based on the patient's history, clinical presentation, signs & symptoms suggesting dengue fever and confirmation was made by performing the blood tests i.e. NS1Ag, Dengue IgM or PCR.

A preformed structured questionnaire was used to collect the relevant data regarding basic demographics (such as age and gender), clinical data (weight, height, basal metabolic index, duration of fever, dose of paracetamol, and periodic AST & ALT levels). The data were evaluated in Statistical Package for the Social Sciences (SPSS) version 21.0 and a p value of <0.05 is considered to be statistically significant.

RESULTS

Out of total 100 patients, there were 56% males and 44% females and overall mean age was 35.21±15.13 years. The overall mean weight, height, BMI, and mean duration of fever in days was 61.13±17.26 kg, 1.60±0.14 meter, 23.85±6.73 kg/m^2, and 4.20±1.43 days, respectively.

Among 100 patients, 63% were confirmed dengue by NS1 AG and 37% by RGM as presented in Table-I. Among them, 27% were treated with ≤2 gm/24 hrs paracetamol and 73% were treated with ≥2-4 gm/24 hrs as shown in Table-II.

In our study, mean AST & ALT and AST/ALT ratio at 1st week were 33.23±23.18 IU/l, 48.52±55.47 IU/l, and 0.83±0.34 IU/l, respectively. While mean AST & ALT and AST/ALT ratio at 3rd week was 33.08±20.59 IU/l, 45.59±17.33 IU/l, and 0.74±0.29 IU/l, respectively.

The results showed that there is significant mean difference between AST/ALT ratio at 1st week and 3rd week ($p=0.010$) as presented in Table-III. The results also showed significant mean difference between AST/ALT ratio at 1st week and 3rd week for 2-4 gm/24hrs of paracetamol used ($p=0.001$) as presented in Table-IV.

Independent t-test also shows significant mean difference of AST/ALT ratio at 1st week ($p=0.001$) as well as at 3rd week ($p=0.020$) according to paracetamol dose as presented in Table-V and Table-VI.

	Frequency (%)
NS1 AG	63 (63%)
RGM	37 (37%)
TOTAL	100

Table-I. Frequency distribution of dengue diagnosis confirmed by. (n=100)

	Frequency (%)
<2 gm/24 hrs	27 (27%)
2-4 gm /24hrs	73 (73%)
TOTAL	100

Table-II. Frequency distribution of paracetamol dose. (n=100)

	Mean	SD	P-Value
AST/ALT Ratio at 1st Week	0.749	0.296	0.010*
AST/ALT Ratio at 3rd Week	0.838	0.349	

Table-III. Mean comparison of ast/alt ratio at 1st week with 3rd week. (n=100)

Paired t-test was applied.
P-value ≤0.05 considered as Significant.
* Significant at 0.05.

Dose	AST/ALT Ratio	Mean	SD	P-Value
<2 gm/24hrs	AST/ALT Ratio at 1st Week	0.603	0.282	0.267**
	AST/ALT Ratio at 3rd Week	0.659	0.184	
2-4 gm/24 hrs	AST/ALT Ratio at 1st Week	0.924	0.332	0.001*
	AST/ALT Ratio at 3rd Week	0.782	0.323	

Table-IV. Mean comparison of AST/ALT ratio at 1st week with 3rd week for paracetamol dose. (n=100)

Paired t-test was applied.
P-value ≤0.05 considered as Significant.
* Significant at 0.05.
** Not Significant at 0.05.

	Mean	SD	P-Value
<2 gm/24 hrs	0.603	0.282	0.001*
2-4 gm/24 hrs	0.924	0.332	

Table-V. Mean comparison of ast/alt ratio at 1st week according to paracetamol dose. (n=100)

Independent t-test was applied.
P-value ≤0.05 considered as Significant.
* Significant at 0.05.

	Mean	SD	P-Value
<2 gm/24 hrs	0.659	0.184	0.020*
2-4 gm/24 hrs	0.782	0.323	

Table-VI. Mean comparison of AST/ALT ratio at 3rd week according to paracetamol dose. (n=100)

Paired t-test was applied
P-value ≤0.05 considered as Significant.
* Significant at 0.05.

DISCUSSION

Paracetamol induced acute liver injury in patients with dengue fever have not been well studied worldwide including Pakistan and some of the authors suggested performing liver functions tests before commencement of paracetamol those who are infected with dengue fever but data reports patients before coming to emergency have already taken paracetamol for the symptoms of fever.[12-14]

A study conducted by Syed AA and colleagues have shown association between ALT in patients taking paracetamol during the illness of dengue fever but it is insignificant and prevalence is less than 11%.[15] These results show that frequency of worsening liver function in patients with severe dengue hepatitis upon receiving paracetamol was relatively low, and may not be directly related to mortality. While on the other hands, observations from our study have shown significant association with doses of paracetamol and change in liver functions tests by the end of 1st week and even by the end of 3rd week. The reason cannot be define based on few observational studies because a great controversy has been shown among our study and a previously conducted studies. Possibly, geographical pattern, genetics, underlying comorbids, health care services, and disease severity could be associated with different outcomes in multiples studies.[16-18] This need to be scientifically proven based on multicentre randomized trials that are lacking worldwide. A study published in the lancet is in agreement with our study and shown the use of paracetamol in patients with dengue significantly increased the incidence of transaminase elevation and also intake of Paracetamol did not affect body temperature, pain score, analgesic intake, length of stay, or duration of fever. More significant effects of transaminase elevations were also found in the per-protocol analysis, which disregarded those who did not receive study medication.

In our study, mean AST & ALT and AST/ALT ratio at 1st week were 33.23±23.18 IU/l, 48.52±55.47 IU/l, and 0.83±0.34 IU/l, respectively. While mean AST & ALT and AST/ALT ratio at 3rd week was 33.08±20.59IU/l, 45.59±17.33IU/l, and 0.74±0.29 IU/l, respectively. Levels of liver enzymes vary in different studies and are not linked with poor patient's outcome. Some of the studies[19-22] have documented less than 3 folds of change in liver enzymes but outcome was poor while on the other hand some studies documented more than 3 folds increase in liver enzymes and were not

associated with documented increase in mortality rate. Based on such varied and inconclusive outcomes liver functions should be determined early, and in cases of prolonged fever, at regular intervals. Gan CS[23] reported a patient who were treated during the hospitalization of dengue fever with paracetamol less than 4gm per day and found to have toxic serum levels of paracetamol that is why it is necessary to administer cautiously paracetamol when it is really needed. On the other hands, it has been reported from observational studies[24-26] that patients with mild illness caused by dengue fever take paracetamol without any recommendation from doctor sometimes the dose is higher than 4gm per day before reaching to hospital which is relatively toxic to the liver and may lead to acute liver injury.

A study published in Sri Lanka[27] consisted of patients who took paracetamol during dengue fever before seeking any medical attention were more likely to develop fulminant hepatic failure or liver failure at the time of hospital admission. Other studies conducted internationally have found prevalent number of cases ranging from 31% – 44% who took more than 4gm of paracetamol dose in a day before presenting to emergency department were developed acute liver injury and their AST and ALT levels were more than 3 times higher than normal and that is why they have recommended use of 2gm per day of paracetamol to prevent from paracetamol induced acute liver injury.

Our study has few limitations such as the data is extracted from the single center and also the numbers of cases that we have included were less. On the other hands, data should be collected for comorbid conditions and associated drug interactions so the biased can be minimized.

CONCLUSION

In our study, results showed significant improvement in AST, ALT, and AST/ALT ratio at 1st week and 3rd week at different doses of paracetamol.

REFERENCE

1. Kulkarni AV, Choudhury AK, Premkumar M, Jain P, Gupta E, Sarin SK. **Spectrum, manifestations and outcomes of dengue infection in individuals with and without liver disease.** J Clin Transl Hepatol 2019 Jun 28; 7(2):106-11.

2. Masyeni S, Yohan B, Sasmono RT. **Concurrent infections of dengue virus serotypes in Bali, Indonesia.** BMC Res Notes 2019 Mar 12; 12(1):129.

3. Al-Tawfiq JA, Memish ZA. **Dengue hemorrhagic fever virus in Saudi Arabia: A Review.** Vector Borne Zoonotic Dis 2018 Feb; 18(2):75-81.

4. Jahan NK, Ahmad MP, Dhanoa A, Meng CY, Ming LW, Reidpath DD, et al. **A community-based prospective cohort study of dengue viral infection in Malaysia: The study protocol.** Infect Dis Poverty 2016 Aug 11; 5(1):76.

5. Haider Z, Ahmad FZ, Mahmood A, Waseem T, Shafiq I, Raza T, et al. **Dengue fever in Pakistan: A paradigm shift; changing epidemiology and clinical patterns.** Perspect Public Health 2015 Nov; 135(6):294-8.

6. Aung KL, Thanachartwet V, Desakorn V, Chamnanchanunt S, Sahassananda D, Chierakul W, et al. **Factors associated with severe clinical manifestation of dengue among adults in Thailand.** Southeast Asian J Trop Med Public Health 2013 Jul 4; 44(4):602-12.

7. Tanner L, Schreiber M, Low JG, Ong A, Tolfvenstam T, Lai YL, et al. **Decision tree algorithms predict the diagnosis and outcome of dengue fever in the early phase of illness.** PLoS Negl Trop Dis 2008 Mar 12; 2(3):e196.

8. Niriella MA, Liyanage IK, Udeshika A, Liyanapathirana KV, Silva PD, Silva Jd. **Identification of dengue patients with high risk of severe disease, using early clinical and laboratory features, in a resource-limited setting.** Arch Virol 2020 Sep; 165(9):2029-35.

9. Ahmed AE, Dahman B, Altamimi A, McClish DK, Al-Jahdali H. **The aspartate aminotransferase/platelet count ratio index as a marker of dengue virus infection: Course of illness.** J Infect Public Health 2020 Jul; 13(7):980-4.

10. Chen D, Zhang Y, Wu X, Wu J, Gong F, Qiao L, et al. **A survey of clinical and laboratory characteristics of dengue fever epidemic from 2014 to 2018 in Guangzhou, China.** Ann Palliat Med 2020 Jan; 9(1):70-81.

11. Prasad D, Bhriguvanshi A. **Clinical profile, liver dysfunction and outcome of dengue infection in children: A prospective observational study.** Pediatr Infect Dis J 2020 Feb; 39(2):97-101.

12. Chia PY, Thein TL, Ong SWX, Lye DC, Leo YS. **Severe dengue and liver involvement: An overview and review of the literature.** Expert Rev Anti Infect Ther 2020 Mar; 18(3):181-9.

13. Kajimoto Y, Kitajima T. **Clinical management of patients with dengue infection in Japan: Results from National Database of Health Insurance Claims.** Am J Trop Med Hyg 2020 Jan; 102(1):191-4.

14. Vasikasin V, Rojdumrongrattana T, Chuerboonchai W, Siriwiwattana T, Thongtaeparak W, Niyasom S, et al. **Effect of standard dose paracetamol versus placebo as antipyretic therapy on liver injury in adult dengue infection: A multicenter randomized controlled trial.** Lancet Glob Health 2019 May; 7(5):e664-e670.

15. Syed AA, Aslam F, Hakeem H, Siddiqui F, Nasir N. **Frequency of worsening liver function in severe dengue hepatitis patients receiving paracetamol: A retrospective analysis of hospital data.** J Pak Med Assoc 2017 Mar; 67(3):400-4.

16. Kellstein D, Fernandes L. **Symptomatic treatment of dengue: should the NSAID contraindication be reconsidered?** Postgrad Med 2019 Mar; 131(2):109-16.

17. Ferreira RAX, Kubelka CF, Velarde LGC, Matos JPS, Ferreira LC, Reid MM, et al. **Predictive factors of dengue severity in hospitalized children and adolescents in Rio de Janeiro, Brazil.** Rev Soc Bras Med Trop 2018 Nov; 51(6):753-60.

18. Syed AA, Aslam F, Hakeem H, Siddiqui F, Nasir N. **Frequency of worsening liver function in severe dengue hepatitis patients receiving paracetamol: A retrospective analysis of hospital data.** J Pak Med Assoc 2017 Mar; 67(3):400-4.

19. Djossou F, Vesin G, Walter G, Epelboin L, Mosnier E, Bidaud B, et al. **Incidence and predictive factors of transaminase elevation in patients consulting for dengue fever in Cayenne Hospital, French Guiana.** Trans R Soc Trop Med Hyg 2016 Feb; 110(2):134-40.

20. Anand AC, Garg HK. **Approach to clinical syndrome of jaundice and encephalopathy in tropics.** J Clin Exp Hepatol 2015 Mar; 5(Suppl 1):S116-S130.

21. Pandejpong D, Saengsuri P, Rattarittamrong R, Rujipattanakul T, Chouriyagune C. **Is excessive acetaminophen intake associated with transaminitis in adult patients with dengue fever?** Intern Med J 2015 Jun; 45(6):653-8.

22. Habaragamuwa BW, Dissanayaka P. **N-acetylcystein in dengue associated severe hepatitis.** Indian J Crit Care Med 2014 Mar; 18(3):181-2.

23. Gan CS, Chong SY, Lum LC, Lee WS. **Regular paracetamol in severe dengue: A lethal combination?** Singapore Med J 2013 Feb; 54(2):e35-e37.

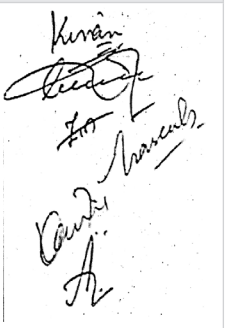
24. Mangold KA, Reynolds SL. **A review of dengue fever: A resurging tropical disease.** Pediatr Emerg Care 2013 May; 29(5):665-9.

25. Gan CS, Chong SY, Lum LC, Lee WS. **Regular paracetamol in severe dengue: A lethal combination?** Singapore Med J 2013 Feb; 54(2):e35-e37.

26. Agarwal MP, Giri S, Sharma V, Roy U, Gharsangi K. **Dengue causing fulminant hepatitis in a hepatitis B virus carrier.** Biosci Trends 2011; 5(1):44-5.

27. Jayadas TTP, Kumanan T, Arasaratnam V, Gajapathy K, Surendran SN. **The clinical profile, hematological parameters and liver transaminases of dengue NS1 Ag positive patients admitted to Jaffna Teaching Hospital, Sri Lanka.** BMC Res Notes 2019 Sep 23; 12(1):604.

AUTHORSHIP AND CONTRIBUTION DECLARATION

No.	Author(s) Full Name	Contribution to the paper	Author(s) Signature
1	Kiran Hafeez	All authors have contributed equally.	
2	M. Akbar Memon		
3	Zia Farooqui		
4	Haseeb Jameel Memon		
5	Kamran Baig Memon		
6	Abdul Aziz		