J Young Pharm, 2020;12(2):153-157
A multifaceted peer reviewed journal in the field of Pharmacy
www.jyoungpharm.org | www.phcog.net

Original Article

Evaluation of Hepatotoxicity of Anti-Tuberculosis Regimens: A Prospective Study in Tribal Population of Central India

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ABSTRACT

Background: The magnitude of tuberculosis (TB) and associated risk factors for development of toxicity to anti-TB drugs in vulnerable tribal groups are useful indicators for understanding extent of TB transmission, effectiveness of TB therapy. Such studies help to gather information, helps in planning control and preventive strategies for TB in this special population. The study was carried out to evaluate incidence of hepatotoxicity, association between risk factors, anti-TB regimen and hepatotoxicity in selected vulnerable population. **Materials and Methods**: Prospective study in tribes (Gond, Halba, Kawar) of a district in central India diagnosed with pulmonary/extrapulmonary/Multi drug resistant TB. These patients were on anti- TB regimen, monitored clinically and biochemically for hepatotoxicity at the end of 1, 3 and 6 months of anti-tubercular therapy. A specific criterion was set for diagnosing hepatotoxicity. **Results:** Incidence of hepatotoxicity was 9.23%. Raised serum transaminase, bilirubin level and symptoms of hepatotoxicity like nausea, anorexia, vomiting, malaise, jaundice, were observed. The onset of hepatotoxicity ranged from 25-180 days (median 65 days). Of various risk factors analyzed, high alcohol intake was associated with hepatotoxicity (odds ratio = 9.3, 95% confidence interval 1.8–47, p=0.003). Age, gender, extent of tuberculosis disease, malnutrition was not significantly associated with anti-tuberculosis treatment hepatotoxicity. Relative risk of developing hepatotoxicity in alcoholic addicted males was 14.117. **Conclusion:** Withdrawal of alcohol habit in selected tribes on anti-Tuberculosis regimen will cause a drop in developing hepatotoxicity by 93%. Mass education regarding same would curtail hepatotoxicity making therapy safe.

Key words: Directly observed treatment shortcourse, Ethambutol, Isoniazid, Pyrazinamide, Rifampicin.

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DOI: 10.5530/jyp.2020.12.31

INTRODUCTION

Tuberculosis (TB) is a world-wide health problem and is one of the top 10 causes of death. In 2016, the WHO estimated that there were 10.4 million cases of TB and 1.7 million deaths due to TB all over the world.[1] India accounts one fourth of world's TB burden. Annual incidence rate of TB in India is around 2 million and around 3,00,000 death occurs due to TB every year in the country.[2] TB leads to loss of productivity causing loss of 20-30% of annual household income. Directly observed treatment short course (DOTS) is the main pillar employed for control of TB under RNTCP (Revised National TB control Program) in India. Isoniazid (INH), Pyrazinamide (PZA) and Rifampicin (RMP) are used in DOTS as the main drugs. They have the potential to cause hepatotoxicity, the incidence of which is reported to be 2-28%.[3] The spectrum of hepatotoxicity ranges from asymptomatic rise in transaminase (upto five-fold) in 2.3-28% to acute liver failure in approximately <0.01% of the individuals.[4] This might result in treatment withdrawal, substitution, dosage regimen adjustment, non-adherence and drug resistance.[5] Ethambutol and streptomycin in the DOTS regimen have different adverse effects profile than hepatotoxicity.[6] A higher risk of hepatotoxicity has been reported in Indian patients than in their western counterparts.[7] There are many factors that contribute to the development of the anti TB drug induced hepatotoxicity. In a study reported by Wond wossen Abera *et al.* it has been shown that history of chronic alcohol intake is a pre disposing factor for anti TB drug induce hepatotoxicity.[8] A study in Taiwan showed that slow acetylators are at a higher risk of developing hepatotoxicity as compared to the rapid acetylators.[9] A study conducted by Rajani Shakya *et al.* revealed that the incidence of anti TB drug induced hepatotoxicity was higher in younger patients.[10] Similar studies noted nutrition, low albumin, high dose acetaminophen intake, female gender, older age and low serum cholesterol as the risk factors.[11] Body mass index [BMI] found to be significantly lower in anti-tubercular treatment (ATT) induced hepatitis patients.[12] However some studies reported that there was no significant association between hepatotoxicity and various factors.[13,14] The risk factors that contribute to the development of anti-TB drug hepatotoxicity are still unclear and controversial. Understanding anti-TB drug hepatotoxicity is restricted to the difference in study populations, definition of hepatotoxicity and monitoring practices.[8] Hence, the present study is planned to evaluate incidence of hepatotoxicity after anti-tubercular treatment and to evaluate association between risk factor, anti-tubercular treatment regimen and hepatotoxicity.

MATERIALS AND METHODS

This was a prospective study carried out for a period of 8 months and 10 days, from 21st Jan to 30th September 2019 in District TB Centre [DTC] and attached Peripheral Health Centres (PHCs) of a tertiary care institute in tribal region of central India. Men and women who were newly diagnosed pulmonary TB [P], extra-pulmonary TB [EP] or multi-drug

resistant [MDR] cases falling in the age group of 18-80 years constituted the study population. A total of 65 patients were included. The study was started after getting approval from the Institutional Ethics Committee (Reg.no.ECR/1033/Inst/MH/2018). The patients were explained the entire procedure of the study in the local language, then patients were asked to sign the informed consent form. The participation and identity were not revealed.

The newly diagnosed TB patients who had serum aspartate Aminotransferase (AST) less than 45 IU/L, serum alanine Aminotransferase (ALT) less than 45 IU/L and total bilirubin less than 1mg/dl were included in the study. Patients who had ALT and AST values greater than two times the upper limit of normal (ULN > 42U/Land 37U/L, respectively) were excluded. Patients positive for hepatitis B surface antigen, anti-HCV antibodies or HIV positive cases were also excluded. Patients not willing to participate, patients receiving any other hepatotoxic drugs were also not considered. Pregnant women were not included in the study.

Initial history of patients diagnosed at DTC was obtained. The participant's information was gathered on a Case Record Form (CRF). The demographic details, diagnosis, anti-tubercular kit and regimen details, history of co-morbid illnesses, history of other drug intake, addiction to alcohol was elicited. Alcohol addiction was defined as a daily consumption of more than 40gm of alcohol for at least five years. After taking the history, complete physical examination was done. The patient's TB status was classified according to the standard guidelines.[15] The Gene Xpert (CB-NAAT), a PCR test was used for diagnosis of TB and to check for rifampicin resistant TB in each patient. The clinically diagnosed patients of TB were subjected to sputum examination. Before the start of treatment in the smear positive cases, the following lab test were done in the Central Clinical Laboratory of the study site-Estimation of blood sugar, Hb, CBC, HIV, HBs Ag, Anti-HCVAb, ALT, AST, Bilirubin [direct and indirect]. Treatment was given according to RNTCP 2016 –guidelines[16]

Pulmonary TB [P]cases were started on Category I regimen - Isoniazid, Rifampicin, Pyrazinamide, Ethambutol. The treatment was for 6 months

Initial phase (IP): Isoniazid, Rifampicin, Pyrazinamide and Ethambutol- for 2 months

Continuous phase (CP): Isoniazid, Rifampicin, Ethambutol- for 4 months.

Extra-pulmonary TB [EP] cases were started on the same regimen as stated above but the treatment was of 12 months.

Initial phase (IP): for 2 months

Continuous phase (CP): for next 10 months

Dose of each patient was decided on the basis of RNTCP weight band

Drug Dosage for Adult TB

Weight category	Number of tablets (FDCs)	
	Intensive phase HRZE* 75/150/400/275	Continuous phase HRE* 75/150/275
25-39 kg	2	2
40-54 kg	3	3
55-69 kg	4	4
≥70 kg	5	5

*H-isoniazid, R-Rifampicin, Z-pyrazinamide, E-Ethambutol

MDR cases

Type of TB case	Regimen in IP	Regimen in CP
R resistant + H sensitive or UK	6-9 months Km LfxE to Cs Z E H	18 mon LFx E to CsEH
R sensitive + H resistant	3-6 mon Km Lfx R E Z	6 mon Lfx R E Z

UK–Unknown IP-Intensive phase

CP-Continous phase

R–Rifampicin, H-Isoniazid, Km -Kanamycin, Lfx –Levofloxacin, E- Ethambutol, Z–Pyrazinamide, Eto -Ethionamide, Cs –Cycloserine.

The follow up procedure of the patient involves:

1. Clinical evaluation: Patients were observed for signs and symptoms of hepatotoxicity like nausea, anorexia, vomiting, malaise, organomegaly or jaundice. Patients were kept under close observation during the study period and were asked to report any unusual signs and symptoms.
2. Lab investigations: The liver function tests were done before the start of treatment and repeated at the end of 1, 3 and 6 months of treatment.

In the present study anti-TB drug induced hepatotoxicity was defined by the presence of any one of the following criteria:[6]

1. A rise to ≥5 times the normal serum level of transaminases (normal serum glutamatepyruvate transaminase or SGPT: 7-41 U/L, normal serum glutamic-oxaloacetate transaminase or SGOT: 12-38 U/L).
2. A rise in the level of serum total bilirubin > 1.47 mg/dL.
3. Any increase in serum transaminase above pretreatment levels together with symptoms of anorexia, nausea, vomiting, and jaundice.

A causal relationship between the anti-TB drugs and hepatotoxicity was made by using the WHO-UMC causality analysis scale.[17] These reactions were reported to the NCC, PvPI.

At the end of 1, 3 and 6 month the empty strips were checked to ensure that the patient has taken his/her proper dose.

Statistical analysis

Analyses were carried out using MS Excel 2010. Data was pooled as count and percentages. The outcome variable was hepatotoxicity. Baseline characteristics of the 65 patient's were described and the characteristics of patients with hepatotoxicity were compared with those without it. Continuous variables were presented as means or medians while the categorical variables were presented as proportions. Comparisons between two means or between two medians were done using paired *t* test. For proportions the test of significance applied was a Fisher Exact Probability test. A p-value<0.05 was considered significant for all tests.

RESULTS

A total of 65 TB patients taking anti-TB drugs participated in this study, 46 (70.76 %) of the respondents were males and 19(29.23%) were females. The mean age of respondents was 39.64± 15.19 years but the highest number of participants were found in the age group of 18-30 years (38.46%). The weight of the participants ranged from 25-70 kg with the mean ± standard deviation value being 50 ± 9.6 kg. [Table 1] The total duration of the study was for 8 months and 10 days. Each patient was followed up for a period of 6 months. Till the completion of study, 54 (83.07%) patients were followed up, 4 (6.15%) died and 7 (10.76%) didn't turn up for follow up.

Among the total 65 participants, 25 (38.46%) were newly diagnosed smear-positive pulmonary (P) TB cases, 27 (41.53%) were extra

Table 1: Demographic and anthropometric data of study participants (n=65).

Characteristics		n *(%)*
Gender	Male	46(70.76)
	Female	19(29.23)
Age (years)	18-30	25(38.46)
	31-40	12(18.46)
	41-50	10(15.38)
	>50	18(27.69)
Weight (kg)	25-39	23(35.38)
	40-54	30(46.15)
	55-69	11(16.92)
	≥70	1(1.53)

Table 2: Type of TB and other characteristics of study participants (n=65).

Characteristics	n (%)
Type of TB	
Pulmonary	25(38.46)
Extra-Pulmonary	27(41.53)
MDR*	13(20)
Diabetic status	
Diabetic	1(1.53)
Non-diabetic	64(98.46)
Alcohol addiction	
Addicted	17(26.15)
Non-addicted	48(73.84)
Outcome of patients in TB units	
Did not turn up for follow up	7(10.76)
Followed till the last date of study (6 months)	54(83.07)
Dead	4(6.15)

*MDR-Multidrug resistance

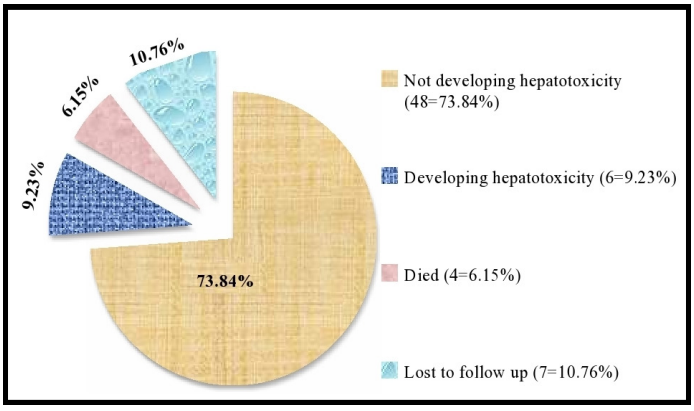

Figure 1: Outcome at the end of 6 months (n = 65).
Note: The incidence of hepatotoxcity in the study population came out to be 9.23%

Table 3: Comparison of type of TB and other characteristics of participants in hepatotoxic and non-hepatotoxic patients (*n*=65).

Variable	Groups	Patients without hepatotoxicity (n=59)	Patient with hepatotoxicity (n=6)	*p* value
Age (years)	18-39	32	1	0.104
	40-80	27	5	
Gender	Males	40	6	0.168
	Females	19	0	
Type of TB	Pulmonary	24	1	0.203
	Extra	25	2	
	Pulmonary	10	3	
	MDR			
Weight (kg)	25-54	48	5	1
	55 and above	11	1	
Alcohol	Present	12	5	0.003*
Addiction	Absent	47	2	

Fisher Exact Probability Test

**p* value <0.05 statistically significant

Note:

❖ The relative risk of developing hepatotoxicity in alcoholic addicted males was 14.117.

❖ Hence we can say that withdrawal of alcohol from the population will cause a drop in developing hepatotoxicity by 93%.

pulmonary (EP) TB cases and 13(20%) were MDR TB cases. Out of 65 patients, 1 patient was diabetic and 17 (26.15%) patients were addicted to alcohol. The characteristics of participants are presented in Table 2 and the outcome of participants till completion of study is presented in Figure 1.

In the present study 6 out of 65 patients developed hepatotoxicity with certainty, which account for 9.23%. For causality analysis WHO–UMC scale was used. The cases developing hepatotoxicity were reported to NCC, PvPI. All the 6(100%) patients were males. The time period for development of hepatotoxicity was as follows: four patients (66.66%) developed in first month, one (16.66%) at the end of 3 months and another one (16.66%) at the end of 6 months. Out of 65 patients, 4 died. The various factors affecting development of hepatotoxicity are shown in Table 3. The base line and peak level values of SGOT, SGPT, direct and indirect bilirubin of respondents participating in the study is presented in Table 4. Clinical signs and symptoms of patients of anti-TB drug induced hepatotoxicity are presented in Table 5.

DISCUSSION

Anti-tubercular drugs are known to cause hepatotoxicity.[10] In the present study sixty-five patients were recruited and started on a particular anti-TB regimen depending on their respective diagnosis as pulmonary/ extra pulmonary /MDR-TB cases. They were followed in both intensive and continuous phase of therapy for a period of 6 months. Cases were followed up at the end of 1, 3 and 6 months of treatment.

In our study 25 (38.46%) participants were of pulmonary TB, 27 (41.53%) extrapulmonary and 13 (20%) MDR TB cases. Out of 65 patients, six developed hepatotoxicity. Out of six, three cases were MDR TB, two extra-pulmonary and one pulmonary TB. There was no statistically significant difference between the type of TB and development of hepatotoxicity. The incidence of anti-TB treatment induced hepatotoxicity

Table 4: Base line and peak level values of liver function test during study in respondents (*n*=54).

Laboratory test	Patients with anti –TB drug hepatotoxicity (n=6) mean ± SEM	*p* value	Patients without anti TB drug hepatotoxicity (n=48**) mean ± SEM	*p*-value
SGPT (U/L)				
Baseline	26.74 ± 12.23	0.000774*	28.66 ± 9.51	3.221
Peak value	99.50 ± 42.50		42.23 ± 13.12	
SGOT(U/L)				
Baseline	31.33± 11.29	0.006694*	32.16± 9.60	7.102
Peak value	99.50 ± 43.23		43.61± 13.47	
Total bilirubin				
Baseline	0.69 ± 0.16	0.003701*	0.90 ± 0.15	6.100
Peakvalue	1.16 ± 0.24		1.08 ± 0.12	

** 48= number of patients not developing hepatotoxicity which are followed till end

Student's paired *t* test

**p*-value < 0.05(Statistically significant)

Table 5: Clinical signs and symptoms in patients of anti-TB drug induced hepatotoxicity (n=6).

Signs and Symptoms	n (%)
Nausea	4(66.67%)
Vomiting	2(33.33%)
Anorexia	5(83.33%)
Malaise	3(50%)

in the present study is found to be to be 9.23%. This finding coincides with the findings from other studies.[1,9,10] However, it is lower than that of a study from Egypt[18] and higher than that of the western world.[1] This variation in the incidence could be due to the differences in patient's characteristics, genetic predisposition, environmental factors, and the difference in criteria of hepatotoxicity.

According to this study, the time interval for the onset of hepatotoxicity after the initiation of treatment was 25–180 days (median- 65 days). Similar findings have been reported in other studies in literature.[5,11] But in some studies the time interval reported is 15-60 days (median -28 or 30 days).[19] This difference could be due to differences in the follow up time of patients.

Advancing age was associated with anti-TB drugs induced hepatitis in many studies.[20] In our study, there was no statistically significant relation between incidence of anti –TB drug induced hepatotoxicity with age distribution of the study group. The probable reason might be that the participants were young with the median age <40 years. These findings are consistent with other studies reported in literature.[21,22] Meta-analysis by some authors suggests that all age groups are at risk for anti-TB drugs induced hepatitis.[1,23]

In the present study, there was no statistically significant difference between incidence of anti –TB drug induced hepatotoxicity with gender distribution. This could be because nearly 2/3rd of participants were males. Sharma SK, Balamurugan A in their study found that 51.7% of patients developing hepatotoxicity were females but it was not statistically significant.[20] Some studies in literature report that women showed four times higher risks of developing hepatotoxicity post anti TB drug treatment.[22,24]

This study showed that the history of alcohol intake was a potential risk factor for anti-TB-drug induced hepatotoxicity and there was statistical significant difference seen between alcoholics and non-alcoholics. The relative risk of developing hepatotoxicity in alcoholic addicted males is 14.117. Hence we can say that withdrawal of alcohol in the said population will cause a drop in developing hepatotoxicity by 93% (Population Attributable Risk). This discrepancy is perhaps due to the maximum number of men participants 46 (70.76%) in our study. Pande JN and collegues in their study reported that the history of alcohol intake was common among the cases.[22,25] On the other hand some studies showed that alcohol intake had no correlation with development of hepatotoxicity.[24] Alcohol consumption is a risk factor ascribed to malnutrition and glutathione store depletion. [22]

Nutritional status which is considered as one of the risk factor for the anti-TB drug induced hepatotoxicity is assessed by body mass-index and serum albumin.[9,24,26] In the present study serum albumin levels of patients could not be measured. 81.53% patients had weight below 54kg. Out of the six hepatotoxic patients 4 (66.67%) had BMI less than18.5kg/m^2. There was no statistically significant difference between incidence of anti–TB drug induced hepatotoxicity with weight distribution of the study group. In malnutrition, glutathione stores are depleted which makes one vulnerable to oxidative injury. In a malnourished person liver metabolizes drug at a slower pace. In a study done in India, incidence of hepatotoxicity was found to be three times higher in malnourished patients.[22]

In the present study elevations of liver enzymes was found in all the cases developing hepatotoxicity and there was statistical significant difference seen in pre and post treatment values of SGOT, SGPT, total bilirubin. All the six patients developing hepatotoxicity had shown gastrointestinal manifestations like nausea, vomiting, abdominal discomfort, anorexia and jaundice. In present study with regards to outcome, 54 (83.07 %) participants followed up till completion of study, 7 (10.76%) did not turned for follow up and 4 (6.15%) died, but we could not co-relate the reason of their death to the disease itself or drug regimen related side-effects. Some studies in literature reported similar findings.[27]

Considering the death cases as Serious Adverse Events (SAE), they were reported to NCC after doing the causality assessment scale using WHO-UMC causality assessment scale.[17]

CONCLUSION

To conclude, the incidence of anti-TB drug regimen induced hepatotoxicity in the study was found to be 9.23%. Of the various risk factors analyzed, only high alcohol intake was associated with hepatotoxicity. The relative risk of developing hepatotoxicity in alcoholic addicted males was 14.117. Hence withdrawal of alcohol habit in the selected tribes on anti-TB regimen will cause a drop in developing hepatotoxicity in them by 93% (Population Attributable Risk). Door step mass education and counseling regarding withdrawal of alcohol in this vulnerable population which is predominant in the region would curtail the hepatotoxicity thus making the anti-TB therapy safe.

ACKNOWLEDGEMENT

We would like to thank the Short Term Studentship Program by the Indian Council of Medical Research (ICMR sts 2019) for giving us a platform to conduct research. The objective of this program is implanting the seeds of research in undergraduate medical students of India.

The above study was done successfully by Mahek S Kewalramani, a III Year MBBS student. The study report was approved by the panel of Experts of ICMR

CONFLICT OF INTEREST

The authors declare no conflict of interest.

Ethical approval

The study was approved by the Institutional Ethics Committee Reg no-ECT/1033/INST/MH/2018).

ABBREVIATIONS

TB: Tuberculosis; **WHO:** World Health Organization; **DOTS:** Directly observed treatment short course; **RNTCP:** Revised National TB control Program; **INH:** Isoniazid; **PZA:** pyrazinamide; **RMP:** Rifampicin; **BMI:** Body mass index; **ATT:** Anti-tubercular treatment; **DTC:** District TB Centre; **PHCs:** Peripheral Health Centres; **P:** Pulmonary; **EP:** Extra-pulmonary; **MDR:** Multi-drug resistant; **AST:** Aspartate Aminotransferase; **ALT:** Alanine Aminotransferase; **ULN:** Upper limit of normal; **CRF:** Case Record Form; **SGPT:** serum glutamatepyruvate transaminase; **SGOT:** serum glutamic-oxaloacetate transaminase; **UMC:** Uppsala Monitoring Centre; **NCC:** National Coordination Centre; **PvPI:** Pharmacovigilance Programme of India.

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Article History: Submission Date : 02-04-2020; Revised Date : 26-04-2020; Acceptance Date : 09-05-2020.
Cite this article: Kewalramani MS, Vaishnao LS, Jaiswal KM, Dudhgaonkar SS, Mahule S, Raghute LB. Evaluation of Hepatotoxicity of Anti-Tuberculosis Regimens: A Prospective Study in Tribal Population of Central India. J Young Pharm. 2020;12(2):153-7.