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Study Of Liver Functional Test Abnormalities Of Bilirubin And Transaminases In Patients Receiving Anti Tuberculosis Treatment Under National Tuberculosis Elimination Programme

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ABSTRACT
INTRODUCTION:
Anti-tubercular medications have been widely used to successfully treat the condition, but despite their effectiveness, there are still many problems that need to be resolved, including the need to manage the side effects of the drugs. One of the often encountered side effects and a significant reason for treatment noncompliance is hepatotoxicity. The degree of severity might range from a straightforward change in the liver's enzymes and acute hepatitis to acute liver failure with a very high death rate.
MATERIALS AND METHODS:
A Prospective, analytical study was carried out on 100 patients with incidence of hepatotoxicity in patients receiving antituberculosis treatment under NTEP in GHCCD, Visakhapatnam.
RESULTS:
Age of patient varied from 14 to 79 years, and male : female ratio was 4:1, All 100 patients were microbiologically diagnosed tuberculosis who were receiving short course for 6 months ATT under NTEP, among 96 were followed up to end of 6 months ,4 were drop outs. a Incidence of hepatotoxicity is 14.5 % , 8 had subclinical hepatitis and 6 had clinical Hepatitis. Mean duration of hepatotoxicity is 12 days. Asymptomatic elevation of bilirubin from baseline in 5%, SGOT in 11 %, SGPT in 9% at the end of 2 weeks. At the end of 4 weeks,2 patients had asymptomatic SGOT elevations,2 had asymptomatic SGPT elevations. All patients were reintroduced on ATT, re-initiation is succesful.
Conclusion:
ATT-induced hepatitis is a typical and occasionally deadly disease. Most often, quitting ATT results in a swift recovery and permits the safe return of drugs after recovery.
Key words : *ATT , hepatotoxicity, Tuberculosis, hepatitis*

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I. INTRODUCTION:

Tuberculosis (TB) has shown to be a concern to the human population in general and underdeveloped countries in particular as a highly contagious infectious illness. The World Health Organization has classified it as a worldwide emergency. TB is a contagious illness that is treatable and preventive. The bacillus that causes tuberculosis, Mycobacterium tuberculosis, spreads when TB patients cough, sneeze, or otherwise release

bacteria into the air. Although it can affect other areas as well, TB mostly affects the lungs. Adults account for 90% of those who get the illness, and men are more likely to be affected than women.

Previously, intermittent regimens were utilized to treat drug-sensitive TB. However, starting in 2017, India adopted daily weight-based FDC medicines for all kinds of TB for 6–9 months. The highest results are being produced by these daily regimens, which have increased treatment adherence. First-line treatment for drug-sensitive tuberculosis, or short course chemotherapy, typically entails a two-month (8-week) intensive phase with four drug FDCs (Isoniazid (INH), Rifampicin (10mg/kg), Pyrazinamide (PYR), and Ethambutol (HRZE), followed by a four-month (16-week) continuation phase with three drug FDCs (Rifampicin, Isoniazid The continuation phase can be prolonged to 5 months, while the intensive phase can be extended to 4 months.

Anti-tubercular medications have been widely used to successfully treat the condition, but despite their effectiveness, there are still significant problems that need to be resolved, including as the requirement for prolonged therapy, the development of multidrug-resistant strains, and some adverse drug reactions. Hepatotoxicity is a side effect that is frequently present and is a significant factor in treatment failure. Hepatotoxicity rates in various trials ranged from even 2% to 75%. Acute hepatitis that progresses to acute liver failure, which has a very high death rate, might present as a simple alteration of liver enzymes and persistent active hepatitis, or it can present as a convoluted picture. Numerous studies conducted around the world have utilized numerous terminologies to describe hepatotoxicity, including DILD (drug-induced liver dysfunction), DILI (drug-induced liver damage),ATLI-Anti tubercular drug-induced liver injury, active hepatitis and Hepatic intolerance. Among the first line drugs Isoniazid, Rifampicin and Pyrazinamide are hepatotoxic. Of these first line drugs,Pyrazinamide is highest hepatotoxic ,followed by Isoniazid and rifampicin the least. Second line Antitubercular drugs with hepatotoxicity are Ethionamide,Prothionamide,Para amino salicylic acid and Rifabutin.

AIMS :

To study the incidence and type of hepatotoxicity in patients taking short course anti tuberculosis treatment under national tuberculosis elimination programme in government hospital for chest and communicable diseases, Visakhapatnam.

OBJECTIVES

To study incidence of hepatotoxicity in patients receiving antituberculosis treatmentunder National tuberculosis elimination programme in Government Hospital for Chestand Communicable diseases, Visakhapatnam

- To analyze various risk factors for the development of hepatotoxicity
- To assess severity of hepatotoxicity in patients
- To study the effect of hepatotoxicity in the follow up

II. Material and Methods :

Study Design: Prospective, analytical study.

Study Population: 100 patients with incidence of hepatotoxicity in patients receiving antituberculosis treatment under NTEP in GHCCD, Visakhapatnam.

Study Period: January 2023 to June 2023 at Government Hospital for Chest and Communicable Diseases, Visakhapatnam.

Inclusion criteria:

1)Patient >14 yrs. of age, male or female, and who are willing to participate in the study.
2)New and previously treated pulmonary tuberculosis patients with microbiologically evident tuberculosis were taken into study.
3) Prescribed to receive antitubercular treatment for pulmonary tuberculosis under national tuberculosis elimination programme(NTEP).
4)Coming in and around Visakhapatnam to minimize drop outs.
5)HIV patients

Exclusion criteria:

1)Patients who are not receiving isoniazid / rifampicin as part of therapy for other illness.
2)Patients with pre-existing acute or chronic liver disease.
3)Patients with fatty liver,cholecystitis,cholelithiasis as diagnosed by ultrasound examination of abdomen.
4)Baseline transaminases more than twice the upper limit of normal range at initial screening.
5)Patients with prior history of hepatotoxicity due to Antitubercular treatment.
6)Using other known hepatotoxic drugs.
7)Pregnant patients

PROCEDURE:

Patients who were diagnosed with pulmonary tuberculosis microbiologically positive, met the inclusion and exclusion criteria, and planned to begin ATT were included in the study. The study was discussed and counseled to the patients. Following receipt of formal confirmation With the patient's and attendees' informed consent, this study was launched. Liver function at its most basic Before beginning ATT on the day of the tests, the above-mentioned parameters were recorded. visit. ATT began in qualified patients. Patients were counseled on the symptoms of hepatic intolerance and encouraged to visit the hospital. Nausea, vomiting, jaundice, altered sensorium, and anorexia are all symptoms. During the follow-up phase, LFTs were collected at 2 weeks, 4 weeks, and 6 months. Isoniazid, Rifampicin, and Pyraziamide are withheld in all hepatitis patients, and LFTs are evaluated within a week.

III. Results :

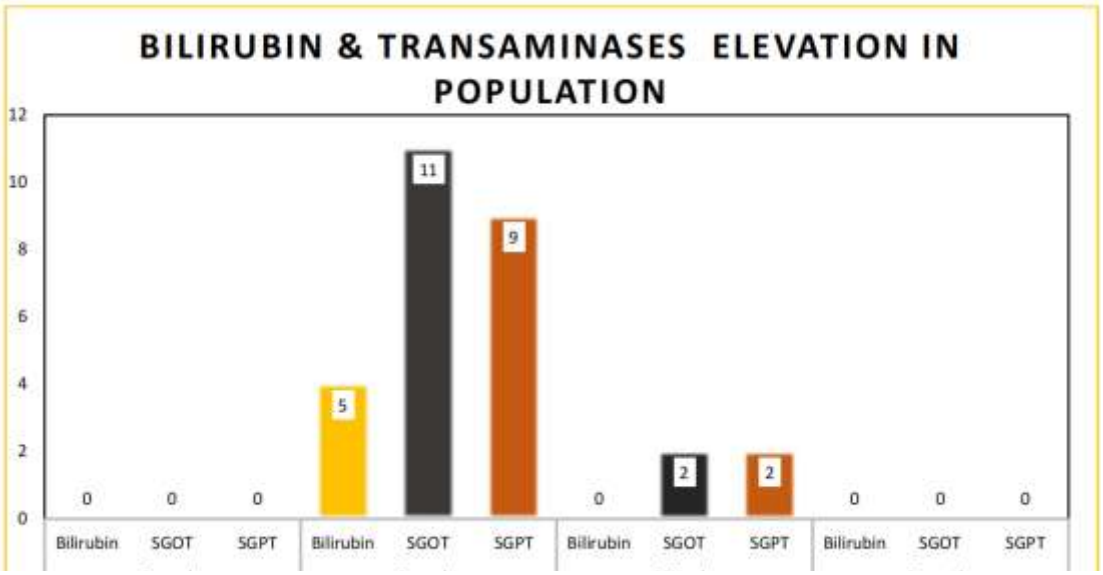
In this study, 100 patients with Pulmonary tuberculosis who were on ATT for six months under the NTEP at the Government Hospital for Chest and Communicable Diseases were enrolled. among 96 patients were completely followed for entire study peroid and 4 were dropout . There were 79 males and 21 females. The study population's mean age is 46 years. About half of these study population had of some comorbidities and 19% had multiple comorbidities. 15% of people reported having PTB in the past. The study group's average BMI was 19.43; 47% of participants were underweight. 73% of people have hypoalbumenia, and 10% of those have severe hypoalbunemia. 16% of people had severe anemia. The most frequent chest x-ray presentation is fibrocavity, followed by nodular opacities. around 51% had a moderately advanced illness on the chest x ray. In our study incidence of Hepatotoxicity is 14.5%, 8 patients had subclinical hepatitis and 6 patients had clinical hepatitis. The most typical sign of hepatotoxicity presentation is vomiting, followed by icterus. Hepatotoxicity is more common in males, and it is more common between the ages of 40-49. Hepatotoxicity mean duration is 12 days (2–28 days). all of the hepatotoxic events took place within a month. asymptomatic patients were showing elevated levels of serum bilirubin in 5% , SGOT in 11%, SGPT in 9% at the end of 2nd week ATT. Two individuals had asymptomatic SGOT elevations and two had asymptomatic SGPT increases at the end of fourth weeks. In our study, we identified serum albumin, BMI, anemia, female gender, and advanced disease on cxr as a hepatotoxicity risk factors. Age, alcohol consumption, and previously treated PTB are not found to be risk factors in this study. All patients were successfully reintroduced to ATT. Hepatotoxicity-related morbidity and mortality were not present in our study.

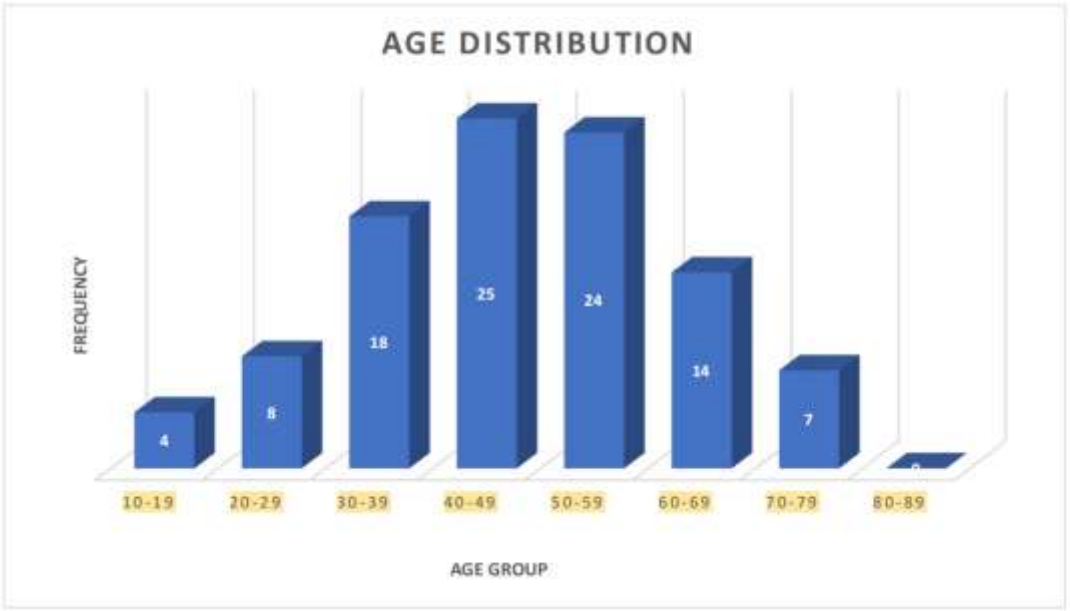
COMPARISION OF SYMPTOMS OF HEPATOTOXICITY IN STUDIES :

Studies	**Most common symptoms**
This study	vomitings
Rajani Shakya	jaundice
Aula abbara	Nausea and vomiting
Sivaraman	jaundice

OUTCOMES OF HEPATOTOXICITY IN STUDY POPULATION :

Outcome - hepatotoxicity patients	
Therapy interruption	14
Discontinued Therapy	0
Prolonged intensive phase duration	14
Drug replacement	0
Change in the route of administration of drug	0
Successful treatment	14





IV. Discussion :

The study was conducted on tuberculosis patients in Visakhapatnam, and the study sample was 100 people, of which 79 were men and 21 were women. In this study, hepatotoxicity is linked to females. they have a higher chance of developing hepatotoxicity with odds ratio of 2.430 (95% CI: 8.23–716), and their relative risk is 2.089. In Gender wise prevalence of Hepatotoxicity, Pharmacodynamics and pharmacokinetics of different medications vary between men and women, which has different efficacy and toxicity consequences. This makes women more susceptible to hepatotoxicity.

In this study, majority of population between the ages of 40 and 49 and followed by age of 50 to 59 years. The study population's mean age is 46. Age had no statistically significant relationship with hepatotoxicity in this study, $p = 0.116$. Age has been cited as a risk factor in numerous research, with a likely reduction in liver function as people age being one of the reasons. However, in this study, age is not a risk factor, and the causes of younger predilection are unknown.

According to the ATS guidelines, the incidence of hepatotoxicity ranged from 5 to 33% in various studies over the world. Comparatively incidence of hepatotoxicity in Indian studies is higher than the western studies. The incidence of hepatotoxicity in this study is 14.28%, which is par with the other studies. Mean duration of hepatotoxicity presentation in our study is 12.14 days with SD 6.35 days. Hepatotoxicity is more common in 1st two months of therapy initiation, reasons are due to hepatic adaptation. In our study symptoms of

hepatotoxicity reported are vomitings(83%), jaundice(66.6%) and nausea(50%). In a study by Rajani Shakya et al. All of the four patients' initial symptoms was jaundice.

In this study, significant bilirubin abnormalities at the end of the second week were found in 5.20% of the population, while SGOT and SGPT abnormalities were found in 11.2% and 9.18% of the population, respectively. Transminases abnormality are 2.06% and 2.09% at the completion of the fourth week. Bilirubin elevation > 5 mg/dl is seen in 13%, milder elevations i.e 1.1 -5gm/dl is seen in 22% . ALT of >51 IU in 15%, 36-50 IU in 4% of the population. AST of >51 IU in 9%, 41-50 IU in 7% of the population. In our study ,severity of disease on chest x ray is a signifacant risk factor for the development of hepatotoxicity and in Gaude G et al, radiographic severity of disease is associated with hepatotoxicity.

In this study previously treated for pulmonary tuberculosis is not a significant risk factor for Hepatotoxicity. penguin shai et al on 4304 TB patients receiving ATT in china, between main and re-treatment TB patients, there was no noticeable difference in the severity of ATLI.

In our study, all of hepatitis patients were successfully re-established and treated with ATT according to ATS guidelines. There were no second event of DILI after re-introduction, there were 4 lost to follow up cases in the study. There were no mortality recorded in our study . this may be due to the early intervention by monitoring in the early 2 months and there by preventing casualities. All were successfully treated with no adverse outcomes.Therapy was prolonged in all 14 patients. There is no effect on sputum conversion in our study. In a study done by Aula Abbara et al on 105 tuberculosis DILI patients, there were 5 of 7 deaths due to DILI which constitute out 4.8 % of the population.

In this study ,anemia is significant risk factor for hepatotoxicity with p value <0.001and serum albumin is significant risk factor for DILI with p =<0.001. In a study done by Rajani Shakya et al, patients with hypoalbunemia had 2 fold risk of developing DILI. In our study , there were no cases of hepatotoxicity after re-introduction of ATT. But In Subramanian natarajan et al, reccurrence of DILI after re-introduction is 10 %.

V. Limitations:

Data for the entire study is gathered from a single location. The dropout rate for this trial is 4%. In our study, we unable to analyze the presence of HIV as a risk factor since there was few HIV patients. This study does not address environmental, genetic, pregnancy, or other host variables for hepatotoxicity.

VI. Conclusion :

In ATT induced hepatitis, the majority of times, discontinuing ATT produces a rapid recovery from hepatitis and allowing for the safe reintroduction of drugs after recovery. Hepatotoxicity and liver abnormalities are more likely in the first month after starting ATT, however timely monitoring of LFTs can lower morbidity and mortality by prompting early drug discontinuation, which leads to better outcome.

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