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RESEARCH ARTICLE

ANTI-TUBERCULAR DRUG INDUCED HEPATOTOXICITY: ASSOCIATED RISK FACTORS UNDER RNTCP-DOTS PULMONARY TUBERCULOSIS PATIENTS.

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Key words:-
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Abstract

Introduction: Prospective study conducted among 263 patients for evaluation of Drug-induced hepatotoxicity (DIH) to know predisposing factors for DIH diagnosed cases of pulmonary tuberculosis patients under anti-tubercular therapy (ATT) as per Revised National Tuberculosis Control Program (RNTCP) on short term regimen at Chatrapati Shivaji Subharti Hospital attached Subharti Medical College, Meerut, Patients attending, Respiratory Medicine Out Patient department (OPD) and referred patients from Urban Health Training Centre and Rural Health Training Centre with pretreatment liver function test (LFT) were assessed.

Patients and methods: Before initiation of first line ATT (Isoniazid, Rifampicin, Pyrazinamide, Ethambutol, and Streptomycin), LFT and other relevant investigations were carried out. Overnight fasting blood samples were collected for LFT on 2nd, 4th and 8th week during treatment for assessment of disease status. A total of 263 patients, 174 male and 89 female with mean age of 41 years were assessed.

Results: A total of 35 patients (13.30%) developed DIH. The Body mass index (BMI) and albumin was found significantly low compared to control ($P<0.01$). The chest radiograph recorded clear cavitory lesions. Results highlight that the age group 41-50 years is at high risk of DIH (31.43%), furthermore it is more prevalent among male (68.57%) than female (31.43%) counterpart.

Conclusion: Old age male, baseline hypoalbuminemia, low BMI, malnutrition and extensive disease states are independent risk factors observed in present study.

Introduction:-

The tuberculosis remains one of the major public health concern in the South- East Asia Region (SEAR), WHO. It is documented that SEAR accounts for 38% of the global burden of tuberculosis (TB) in terms of incidence. It is estimated that about 3.4 million new cases of TB occur every year and about 4, 40, 000 people died of this disease in

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2013. In India, the TB prevalence is showing a steady and important declining trend since 2000; by 2013 the best estimate of prevalence fell under the target of 50% reduction of 1990 level by 2015 [1]. Treatment of tuberculosis requires more than one drug combination. First line anti-TB drugs used in combination to eradicate the infectious disease are isoniazid (INH), rifampicin (RIF), pyrazinamide (PZY), ethambutol (EMB) and streptomycin (STR). These drugs in combination are responsible for drug induced hepatotoxicity (DIH). INH, RIF and PZY have been proved to be highly effective but hepatotoxic [2]. Anti-TB drug administration induced hepatotoxicity is the most common side-effect leading to interruption of therapy [3]. Wide variations have been found in the reported incidence of hepatotoxicity during short-course chemotherapy [4]. A higher risk of hepatotoxicity has been reported in Indian patients than in their Western counterparts [5]. The absence of overt jaundice, the degree of subclinical hepatotoxicity has to be determined by monitoring the biochemical changes using the liver function tests (LFT) [6]. Several risk factors for hepatotoxicity have been suggested such as advanced age, sex, poor nutritional status, liver disease, inappropriate use of drugs, infection with hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV), acetylator status, and chronic alcoholic intake [7].

Patients and Methods:-

The present study was carried out at Subharti Medical College Chatrapati Shivaji Hospital Meerut from May 2014 to April 2016.A total of 281 patients (180 male, 101 female) who are permanent resident of study areas in the age group of 20-70 years with mean age 41 years were followed up for treatment and biochemical markers by 2^{nd}, 4^{th} and 8^{th} week evaluation. Total 18 patients (06 male, 12 female) were dropped out from the study (05 patients by 2^{nd} week, 04 patients by 4^{th} week and 09 patients by 8^{th} week) could not turned up for follow up and treatment. Thus, remaining 263 patients of which 174 male (66.15%) and 89 female (33.84%) were followed up for 08 weeks. All newly diagnosed active pulmonary TB patients were screened for HIV, hepatitis B surface antigen (HbsAg) and HCV antibodies assays. Patients with one or two sputum samples positive for acid-fast bacilli (AFB) by direct microscopy diagnosed as having smear positive pulmonary tuberculosis. Chest X-ray was undertaken in the smear negative pulmonary tuberculosis patients to avoid the delay in diagnosis. Biochemical investigations namely Aspartate amino transaminase (AST), Alanine amino transaminase (ALT), Alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), Total serum protein (TP), serum Albumin, total and direct Bilirubin levels were assayed. Patients having AST/ALT levels >40 IU/L or serum total Bilirubin >1.1mg/dl were excluded from the study. All patients were evaluated for height and weight, BMI calculated and expressed in Kg/m^2. Complete hemogram was also assayed for every patient. All pulmonary tubercular patients were kept on Short course (6 months) antituberculous regimen. This consisted of daily four drugs combination for duration of 2 months i.e. INH, RIF, PZY and EMB; followed by daily INH, RIF and EMB in same doses for additional 4 months. All Patients were followed up all regular intervals for 2^{nd}, 4^{th} and 8^{th} week. Clinical findings and LFT were performed on every follow up. Detailed Patient's profile, such as: name, age, sex, location, literacy, ethnic group, socio-economic status, life style, diet pattern and any concurrent disease and medications other than antitubercular drugs which the patient might be taking, were recorded. The DIH was diagnosed if ALT/AST levels increased up to 5 times or more than upper limit of normal i.e. 40IU/L and no other apparent cause for the elevation of LFT were noticed. If the patient developed DIH, anti tubercular treatment was withdrawn until ALT/AST normalized.

Statistical analysis:-

Patients and control subjects were compared using Student's t-test. Results were declared statistically significant where $p<0.01$ and 95% confidence intervals with 5% level of significance. The statistical analysis was performed using Graph-pad software.

Results:-

Out of 263 patients included in the study, only 35 (13.30%) patients reported DIH of which, 24 male (68.57%) and 11 were female (31.43%). The age group (41-50) years in male (n=09), 37.5% and (51-60) years in female (n=05), 45.44% showed the maximum occurrence of DIH, followed by (51-60) years in male (05), 20.88% and (61-70) years in female (02), 18.18%. The age group (31-40) years in both male (02) and female (02) showed the least occurrence of DIH. Among them, 1.16% (n=03) developed overt hepatitis. The present study highlighted that males are at higher risk than female counterpart for development of DIH.

Discussion:-

A total of 263 patients who were AFB positive for pulmonary tuberculosis, administered category - 1^{st} regimen of RNTCP-DOTS i.e. INH, RIF, PZY and EMB for initially two months followed by INH and RIF for next four

months. All patients were administered these drugs thrice in a week. The incidence of DIH was observed maximum in the age group of 41-50 years, followed by 51-60 years and above. The hepatotoxicity was noted in 32 patients (22 male and 10 female). An overt hepatitis occurred in 03 patients (02 male and 01 female). Literature reports highlight that the female patients are susceptible to hepatitis but in present study it was observed that males are [9] clinically at higher risk of developing hepatitis. Subclinical hepatotoxicity was more common in male than female. A total of 19 hepatotoxic patients (12 male and 07 female) had hypoalbuminemia (Albumin <3.5 g/dl). Krishnaswamy reported that under nutrition contributes to DIH by various mechanisms [10]. Toxicity and over doses are more likely to occur even with the normal dosage of medicine in the presence of low level of serum albumin. Present study correlates with the findings reported by Mehta [11]. Patients who developed clinical hepatitis had severe infection of lungs with tubercular bacilli which was diagnosed by chest X-ray. Subclinical hepatotoxicity occurred in patients of both mild and moderate chest X-rays. None of the patient was found positive for HbsAg or HCV antibody. Hepatitis B and C virus patients are prone to develop DIH [12]. The incidence of hepatotoxicity due to combination of chemotherapy has been reported from 4% to 39% [13] but present study has incidence of 13.30%. Reassessment of LFT was assessed for every patient during 2^{nd}, 4^{th} and 8^{th} week respectively. Elevated levels ALT/AST and serum total Bilirubin activity which occur latter (usually more than 30 days) has been attributed to pyrazinamide while early inclination in LFT (usually less than 14 days) has been attributed to isoniazid and Rifampicin. Isoniazid toxicity is more common in first few weeks of therapy. Clinical and sub clinical hepatitis occurred in less than 4 weeks. Generally asymptomatic hepatitis is more common than clinical hepatitis. Patients with clinical hepatitis had jaundice and elevated levels of ALT, AST and ALP above the 5 folds of the normal range. Total Serum Bilirubin reported higher in 18 patients, out of which 13 patients had less than 4 mg/dl whereas 04 patients were above 4mg/dl. After withdrawal of drug the LFT returned to normal level. Some researchers are of the opinion that patients who developed symptomatic hepatitis do not warrant withdrawing of drugs [14]. But there are reports of hepatic failure and death. Withdrawal of drugs till elevated level of enzyme decline to normal level is advisable [15]. All the drugs were withdrawn in both symptomatic patients. Drugs were re-introduced after normalization of liver enzymes, as all are very effective bactericidal drugs. None of the patient developed any reaction on drug re-introduction and these drugs were prescribed. Patients were discharged with a caution and advice to get admitted again if any symptoms reoccur. Patients who developed symptoms of hepatitis were screened for Hepatitis A, D, E viruses, Hepatitis B antigen, anti HCV antibody and found negative. The patients were strictly kept on prescribed medications for pulmonary tuberculosis i.e. hepatotoxic anti-tuberculosis drugs, it is concluded that the hepatitis is due to drug toxicity. The subclinical hepatitis which is indicated by elevated levels of serum enzyme five times the upper limit i.e., >40 IU/L, was observed in 23 patients and elevated total serum Bilirubin levels, i.e. >1.1 mg/dl was observed in 18 patients. The overt hepatitis was reported only in 03 patients. The incidence of asymptomatic DIH was reflected by elevated serum enzymes is (7.51%)and similarly the incidence of elevated total serum Bilirubin levels is (2.33%).The incidence of clinical hepatitis was (1.16%). A statistically significant correlation observed between age group, sex, severity of chest X-ray, hypoalbuminemia and BMI. Increase in serum enzymes above five folds of normal range was observed in following pattern: 4 patients on 2^{nd} week, 15 patients on 4^{th} week, and 01 patient on 8^{th} week respectively. Increase in serum Bilirubin was noted in 02 patients on 2^{nd} week and 13 patients on 3^{rd} week. Among the patients who developed jaundice were: 01 patient after 02 weeks and 02 patients after 04weeks respectively.

Conclusion:-

The incidence of DIH in patients receiving anti-tubercular drug is 13.30%. The Peak incidence of ATT induced liver damage occurred between third and fourth week of therapy. Patients in the age group of 41-50 years and above are 3.38 times more likely to have DIH than patients in the age group of less than 40 years. The male subjects are at 2.18 times more risk to DIH as compared to female counterparts. Patients with BMI < $18kg/m^2$ are1.7 times at higher risk of developing ATT induced DIH. Patients with basal pretreatment hypoalbuminemia are at higher risk of developing ATT induced DIH. Patients presenting with radiologically severe disease are 2.19 times more likely to develop ATT induced liver damage. The present study highlights advancing age, low BMI, radiologically severe disease and pretreated hypoalbuminemia are independent risk factors for development of ATT induced hepatotoxicity.

Ethical clearance:- Ethical clearance has been obtained from institute's ethical committee (IEC) of Swami Vivekanand Subharti University, Subharti Medical College Meerut.

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Table-I: Comparison of baseline clinical chemistry parameters control and patient.

Sr. no.	Parameters	Control (n=228)	Patients (n=35)	p value
1.	Age (in Years)	40.43 ± 12.04	47.26 ± 12.60	0.0021*
2.	BMI (Kg/m^2)	19.04 ± 2.42	17.73 ± 2.57	0.0034*
3.	Total serum Bilirubin (mg/dl)	0.77 ±0.16	1.38 ± 0.63	0.0001*
4.	Serum total protein (g/dl)	6.57 ± 0.51	6.02 ± 1.84	0.0003*
5.	Serum Albumin (g/dl)	3.69 ± 0.39	2.98 ± 0.35	0.0001*
6.	Serum AST (IU/L)	24.13 ± 6.48	24.42 ± 5.21	0.8009**
7.	Serum ALT(IU/L)	24.0 ± 6.39	25.0 ± 5.64	0.3825**
8.	Serum ALP (IU/L)	64.63 ± 18.13	68.66 ± 18.61	0.1810**

***statistically significant at 95 % confidence interval**

****statistically insignificant at 95 % confidence interval**

Table II - Comparison of LFT between control and patient in 2nd week.

Sr. No.	Parameters	Control(n=228)	Patients(n=35)	P value
1.	Total serum Bilirubin (mg/dl)	0.85 ± 0.16	1.09 ± 0.12	0.0001*
2.	Serum Albumin (g/dl)	3.60 ± 0.49	3.02 ± 0.36	0.0001*
3.	Serum AST (IU/L)	32.69±16.48	67.0±20.20	0.0001*
4.	Serum ALT(IU/L)	34.26±23.37	82.97±36.26	0.0001*
5.	Serum ALP (IU/L)	73.68±26.76	108.48±41.82	0.0001*

***statistically significant at 95 % confidence interval**

Table III: Comparison of LFT between control and patients in 4th week.

Sr. No.	Parameters	Control(n=228)	Patients(n=35)	P value
1.	Total serum Bilirubin (mg/dl)	0.88 ± 0.33	1.40 ± 0.64	0.0001*
2.	Serum Albumin (g/dl)	3.6 ± 0.42	3.15 ± 0.36	0.0001*
3.	Serum AST (IU/L)	41.73±48.03	128.0±97.42	0.0001*
4.	Serum ALT(IU/L)	47.79±68.44	167.88±135.45	0.0001*
5.	Serum ALP (IU/L)	80.17±32.99	133.33±49.03	0.0001*

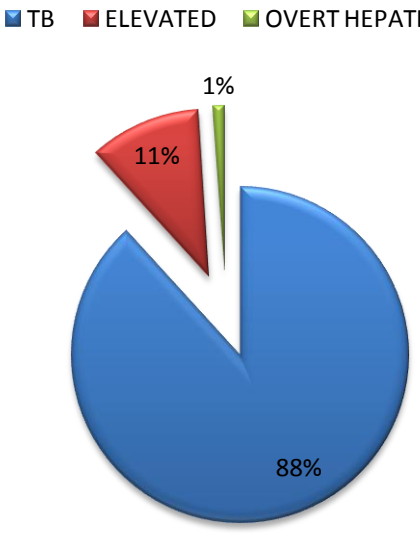
***statistically significant at 95 % confidence interval**

Table IV: Comparison of LFT between control and patients in 8th week.

Sr. No.	Parameters	Control(n=228)	Patients(n=35)	P value
1.	Total serum Bilirubin (mg/dl)	0.86 ± 0.26	1.13 ± 0.29	0.0001*
2.	Serum Albumin (g/dl)	3.7 ± 0.38	3.27 ± 0.31	0.0001*
3.	Serum AST (IU/L)	35.13±17.08	69.37±21.52	0.0001*
4.	Serum ALT(IU/L)	35.25±19.46	75.88±25.37	0.0001*
5.	Serum ALP (IU/L)	75.54±19.52	99.8±25.56	0.0001*

***statistically significant at 95 % confidence interval.**

Fig.1: Incidence of sub-clinical, overt hepatotoxicity



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