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A STUDY OF PERVASIVENESS OF HEPATOTOXICITY AND OTHER SIDE EFFECTS OF ANTI-TUBERCULOSIS DRUGS ON PULMONARY KOCH PATIENTS.

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Abstract:

Tuberculosis (TB) is an infectious disease caused by the bacterium Mycobacterium tuberculosis. About 10% of latent infections progress to active disease which, if left untreated, kills about half of those infected. In immunocompetent individuals, exposure to M tuberculosis usually results in a latent/dormant infection. Only about 5% of these individuals later show evidence of clinical disease.The three key drugs, isoniazid, pyrazinamide and rifampicin, used in the regimen are said to be potentially hepatotoxic and may lead to drug-associated hepatitis. The clinical relevance of therapeutic monitoring of serum rifampicin and isoniazid concentrations in managing antituberculosis drug-associated toxicity is still being explored.So as to identify the potential side effects of those drugs a Prospective,observational study was carried out in Krishna Institute of Medical Sciences (KIMS) hospital at the outpatient department (OPD) of Pulmonology among forty nine patients. Prescriptions, OPD cards and measurement of required parameters were the sources of data. In this study inclusion criteria involves patients of age groups 18-80 years including only outpatients, Patient with/without co-morbidities.The Exclusion criteria involves Patients not willing to give consent, Pregnant and lactating women. Out of total number of patients Males were 21 whereas Females were 28.According to Study conducted it was reported that prevalence and proportion of side effects was different among Men and Women. In Females 22.81% were reported with side effects of vomiting, 22.81% with diarrhea 17.54% with joint pain ,10.53% with skin rash, 22.81% with headache, and 3.51% were reported with Hepatotoxicity .Whereas in Males 25% reported to experience vomiting, 25% with diarrhea, 15% with headache,15% with joint pain and skin rashes and merely 5% were reported with side effect of hepatotoxicity. Thus this study revealed that the Hepatotoxicity appears to be more prevalent in Male subjects than Females which may give a base to the further studies to address a question why Male candidates are prone to hepatotoxicity than their counter gender.

Keywords: *Hepatotoxicity, Anti-tuberculosis drugs, hepatotoxicity,Vomiting, Diarrhoea*

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INTRODUCTION:

Tuberculosis (TB) is an infectious disease caused by the bacterium Mycobacterium tuberculosis (MTB). It commonly affects the lungs, but can also affect other parts of the body. If it does not have symptoms, it is known as latent tuberculosis. About 10% of latent infections progress to active disease which, if not treated, kills about half of those infected. The main cause of TB is Mycobacterium tuberculosis (MTB), a small, aerobic, nonmotile bacillus.(1)

The following factors help to determine whether a TB infection is likely to be transmitted:

1) Number of organisms expelled
2) Concentration of organisms
3) Length of exposure time to contaminated air
4) Immune status of the exposed individual

Infected persons living in crowded or closed environments pose a particular risk to non-infected persons. Approximately 20% of household contacts develop infection (positive tuberculin skin test). Microepidemics have occurred in closed environments such as submarines and on transcontinental flights. Populations at high risk for acquiring the infection also include hospital employees, inner-city residents, nursing home residents, and prisoners.

The following factors increase an individual's risk of acquiring active tuberculosis:

1) HIV infection, Intravenous (IV) drug abuse, Alcoholism, Diabetes mellitus (3-fold risk increase), Silicosis, Immunosuppressive therapy, Tumor necrosis factor–alpha (TNF-α) antagonists, Cancer of the head and neck, Hematologic malignancies, End-stage renal disease, Intestinal bypass surgery or gastrectomy, Chronic malabsorption syndromes
2) Low body weight - In contrast, obesity in elderly patients has been associated with a lower risk for active pulmonary TB
3) Smoking - Smokers who develop TB should be encouraged to stop smoking to decrease the risk of relapse.(2)

Infection with *M tuberculosis* results most commonly through exposure of the lungs or mucous membranes to infected aerosols. Droplets in these aerosols are 1-5 µm in diameter; in a person with active pulmonary TB, a single cough can generate 3000 infective droplets, with as few as 10 bacilli needed to initiate infection.When inhaled, droplet nuclei are deposited within the terminal airspaces of the lung. The organisms grow for 2-12 weeks, until they reach 1000-10,000 in number, which is sufficient to elicit a cellular immune response that can be detected by a reaction to the tuberculin skin test. When a person is infected with *M tuberculosis*, the infection can take 1 of a variety of paths, most of which do not lead to actual TB. The infection may be cleared by the host immune system or suppressed into an inactive form called latent tuberculosis infection (LTBI), with resistant hosts controlling mycobacterial growth at distant foci before the development of active disease.(3)

It is difficult to estimate the incidence of hepatotoxicity due to individual agents as majority of patients is on combination of medications throughout the course of anti-TB therapy. While isoniazid, rifampicin and pyrazinamide are known to cause hepatotoxicity, ethambutol and streptomycin are considered not to be hepatotoxic. Information related to hepatotoxicity from isoniazid (INH), rifampicinand pyrazinamideare derived from observations made during monotherapy for latent TB or when these drugs were combined with apparently non-hepatotoxic medications. INH is the most common drug associated with toxicity. Four large population based observational studies have shown that the incidence of isoniazid hepatotoxicity when used as monotherapy (in treatment of latent infection) to be in the range of 0.1%–0.56%. A review based on the data from U.S. Food and Drug Administration (FDA) estimated that 23.2 per 100,000 people die receiving INH based prophylactic therapy. In a meta-analysis, isoniazid was more likely to be associated with hepatotoxicity (odds ratio (OR) 1.6) even in the absence of rifampicin, but the combination of these two drugs was associated with higher rate of hepatotoxicity (OR 2.6) when compared to each drug on its own.(4) The contribution of pyrazinamide to the development of drug-induced hepatotoxicity during treatment of TB appeared to be controversial in earlier reports.However, later studies or analyses, especially themore recent ones, have been more in favour of pyrazinamide's potential hepatotoxicity, among the various components of a short-course antituberculosis drug regimen.(5)

Objective To determine the rate of isoniazid hepatotoxicity .

MATERIALS AND METHODS:

A prospective, observational study was carried out at the outpatient department (OPD) Pulmonolgy, at Krishna Institute of Medical Sciences (KIMS), Secunderabad over a period of six months. Inclusion criteria involves Patient from pulmonology department only outpatients**,**Both the gender of age groups18-80years**,**Patient with or without co-morbidities**.**Exclusion criteria was Patients not willing to give consent, Pregnant and lactating women. All the relevant and necessary data was collected from patients, using prescriptions, interview with patients and/or their care takers. The collected data includes patient's case notes or OPD card,

treatment charts, laboratory investigations and patient known allergies.

RESULTS:

Table 1: Gender Wise Distribution

GENDER	COUNT
Female	28

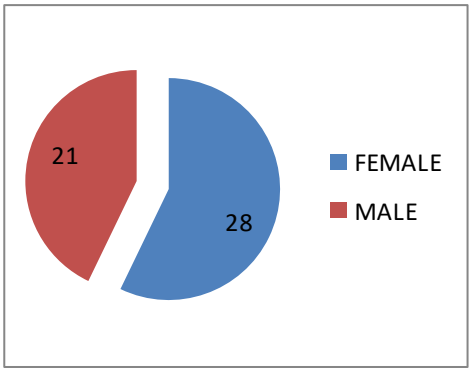


Fig. 1:Gender Wise Distribution

Out of 49 subjects female subjects are found to be 28 and Male subjects are found to be 21.

Table 2: Age Distribution

Age	Male	Female
18	0	1
20-30	3	10
31-40	6	7
41-50	3	2
51-60	4	6
60-70	4	2
71-80	1	0

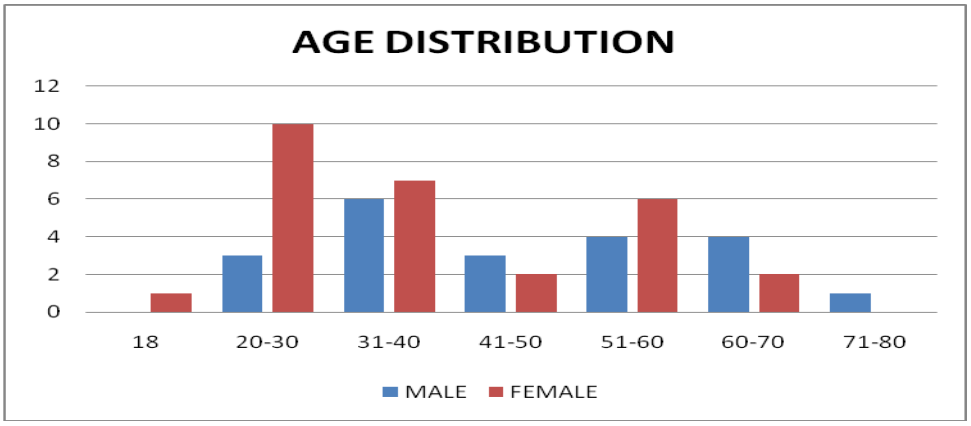


Fig. 2: Age Distribution

Table 3: Side Effects in Female

Vomiting	Diarrhea	Joint Pains	Skin Rash	Hepatotoxicity	Headache
22.81%	22.81%	17.54%	10.53%	3.51%	22.81%

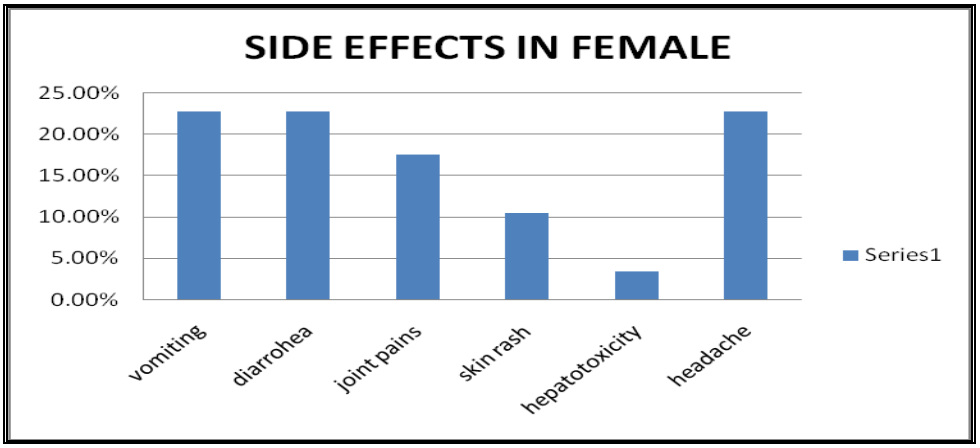


Fig 3: Side Effects in Female

In Females 22.81% were reported with side effects of vomiting,22.81% with diarrhea 17.54% with joint pain ,10.53% with skin rash, 22.81% with headache, and 3.51% were reported with Hepatotoxicity.

Table 4: Side Effects In Males

Vomiting	Diarrhea	Joint Pains	Skin Rash	Hepatotoxicity	Head Ache
25.00%	25.00%	15.00%	15.00%	5.00%	15.00%

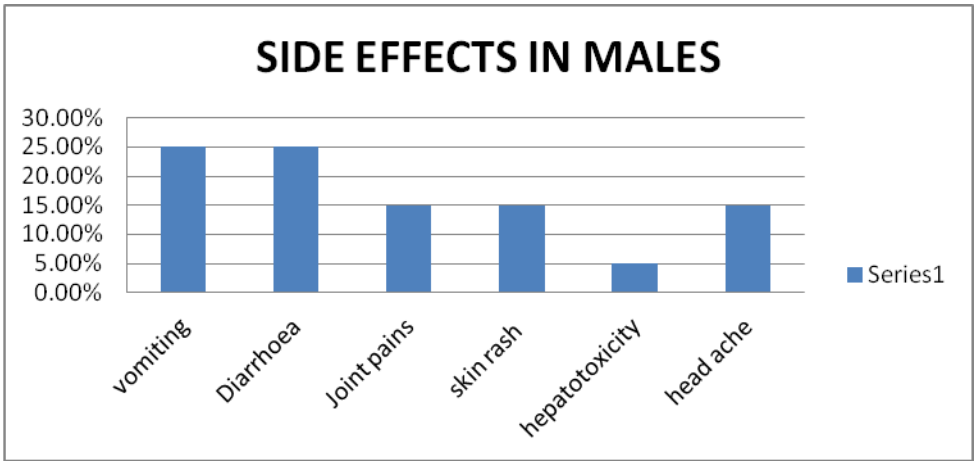
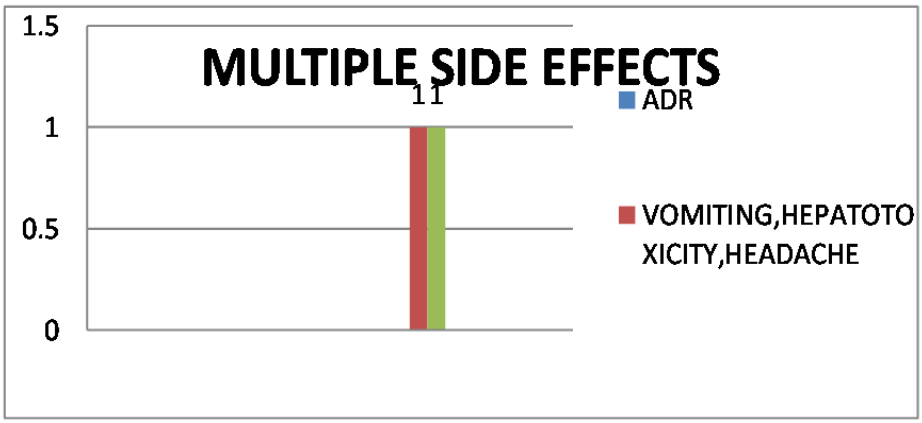


Fig 4: Side Effects In Males.

In Males 25% reported to experience vomiting, 25% with diarrhea, 15% with headache,15% with joint pain and skin rashes and merely 5% were reported with side effect of hepatotoxicity.

Side Effects	No of Patients
Vomiting,Hepatotoxicity,Headache	1
Vomiting,Skin Rash,Hepatotoxicity	1

Table 5: Multiple Side Effects:



In the above Figure only one patient had experienced multiple adverse drug reaction ie vomiting, hepatotoxicity, headache and one patient had side effects of vomiting, skin rash, and hepatotoxicity.

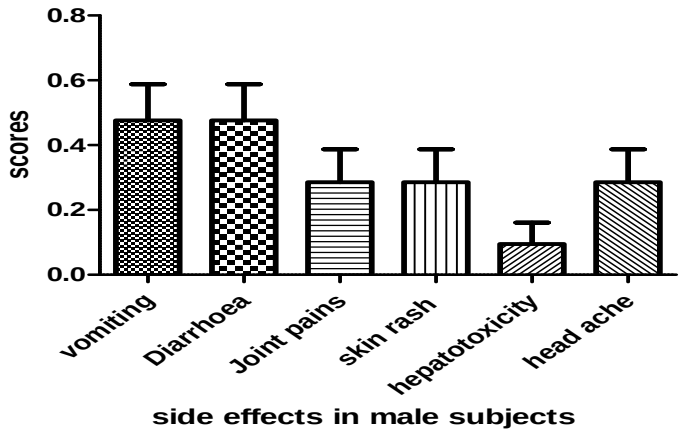


Fig 6: Values are expressed in mean±SEM

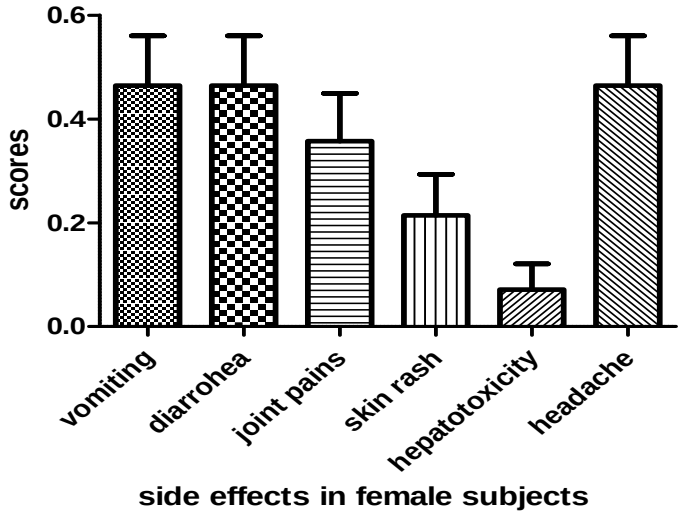


Fig 7: Values are expressed in mean±SEM

DISCUSSION:

The current clinical research study had been conducted at KIMS hospital, Secunderabad on 49 subjects at pulmonology department to study on hepatotoxicity and other side effects of anti-tuberculosis drugs.The Hepatotoxicity Side effects appears to be more prevalent in Male subjects than Female subjects.The Comparision between Males and females with respect to other side effects was found to be 22.81% Vomiting &22.81%Diarrhoea in Female subjects, where as Male subjects are found to be 25.0% Vomiting & 25.0% Diarrhoea Respectively. The other side effects like joint pains are found to be 17.54% in female subjects and 15.0% in male subjects, Skin rash in female subjects are found to be 10.53% where as in male subjects are found to be 15.0%, Headache in female subjects are found to be 22.81% where as in males it is found to be 15.0% respectively.Other were Vomiting (22.81%), Diarrhoea (22.81%) and Headache (22.81%) in Female subjects, where as in males Vomiting (25.0%) and Diarrhoea (25.0%) were noted.

CONCLUSION:

Tuberculosis (TB) is an infectious disease caused by the bacterium Mycobacterium tuberculosis. The three key drugs, isoniazid, pyrazinamide and rifampicin, used in the regimen are said to be potentially hepatotoxic and may lead to drug-associated hepatitis. The clinical relevance of therapeutic monitoring of serum rifampicin and isoniazid concentrations in managing antituberculosis drug-associated toxicity is still being explored.So as to identify the potential side effects of those drugs a Prospective,observational study was carried out.The study revealed that the Hepatotoxicity appears to be more prevalent in Male subjects than Females which may give a base to the further studies to address a question why Male candidates are prone to hepatotoxicity than their counter gender.

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