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A Prospective Study on Treatment Outcomes and Safety Parameters of Anti Tubercular Regimen in Tuberculosis

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A B S T R A C T

Tuberculosis is highly prevalent in developing countries of Asia, Africa and South America, caused by tubercle bacillus. The mycobacterium agents also cause this infection like M. bovis, M. africanum, M. microti, M. caprae, M. pinnipedii, M. canetti and M. mungi. Clinical manifestations depends on few host related factors like age, malnutrition, Study was conducted in TB clinic, Dodla Subba Reddy Hospital, Nellore, Andhra Pradesh, India, visiting the TB clinic, were screened clinically and diagnostically for TB disease, The blood sample were collected before and after 4 weeks after initiation of therapy, Nephrotoxicity can be assessed by the measurement of serum creatinine levels before and after 4 weeks of the initiation of the therapy and difference of the mean values of creatinine before initiation and after 4 weeks of initiation of therapy is determined. Mean values of creatinine before and after the therapy was found to be as 0.9 and 1.2 which was found to match with the study conducted by Sandor Klis on streptomycin in treating other disease condition which showed the development of nephrotoxicity within 4 weeks of the treatment of 9% in 41 patients. Our study also evaluated hematological toxicities which evaluated parameters of hemoglobin, Neutrophils and ESR and these depicted the development of anemia and the mean values was found to be of 9 gm%.

Keywords: Tuberculosis, Nephrotoxicity, ESR, anemia.

A R T I C L E I N F O

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1. Introduction

Tuberculosis is highly prevalent in developing countries of Asia, Africa and South America. It is the commonest cause of death and illness in these regions. Causative organism is tubercle bacillus (mycobacterium tuberculosis) which is a rod-shape, non-motile organism and is highly resistant to adverse conditions of the environment. Thus, it can remain alive in dust for several months. Other mycobacterium agents also cause this infection like M. bovis, M. africanum, M. microti, M. caprae, M. pinnipedii, M. canetti and M. mungi [5].

Types of tuberculosis

1) Pulmonary Tuberculosis
2) Extra pulmonary Tuberculosis

Clinical Manifestations

Clinical manifestations depends on few host related factors like age, malnutrition, immunization, BCG vaccination, genetic factors, co-existing diseases. It also depends on tropism by bacteria to specific tissue, virulence of microorganism. It also depends on host microbe interactions like sites involved, severity of disease.

Study site:

Study was conducted in TB clinic, Dodla Subba Reddy Hospital, Nellore, Andhra Pradesh, India.

Screening:

Patients visiting the TB clinic, were screened clinically and diagnostically for TB disease. Of these patients, patients only with history of TB were recruited over period of time. Various diagnostic tests were done to sort out TB disease in patients.

Subject Eligibility

Inclusion Criteria

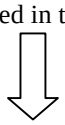
- Persons who come to TB clinic with history of chest pain, whooping cough, sputum and blood in sputum were recruited.
- Patients of both sexes from age 5 years to 50 years.
- Sample were restricted to people who were not receiving prior anti tubercular treatment.

Exclusion Criteria

- The patients should not be on any other potentially hepatotoxic drug and should not consume alcohol.
- IgM anti-HAV, HBsAg, and IgM anti-CMV patients were excluded
- Pregnant women, Elderly patients, HIV infected patients.
- Subjects who were unable to comply with study and diagnostic procedures.

2. Materials and Methods

Tuberculosis was determined in the recruited patients



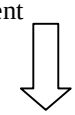
Symptoms and clinical features of patients were noted

Different tuberculosis patients who were prescribed with four drug routine regimens of Isoniazid, Rifampicin, Ethambutol, and Pyrazinamide were recruited and their demographic details, social, family and past medical history were collected.

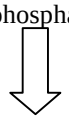
Different drug dosages especially that of INH and Rifampicin and also different drug combinations were noted.

Serum levels of aspartate aminotransferase (ASAT), Alkaline Phosphatase, bilirubin were assessed before initiation of treatment.

Telephonic follow up was done to know if any adverse drug reactions were developed in the patients after administration of treatment



After four weeks of anti tubercular treatment or when the patient develops any symptoms of hepatotoxicity, ASAT, Bilirubin and Alkaline phosphatase levels were measured.



Ruling out the exact drug that caused ADR was done.

This Pattern of assessment is followed in all the patients who were administered with different dose of anti tubercular drugs in combination and alone

3. Results

- One-way ANNOVA and Unpaired student t- test were used for calculating mean, standard deviation, and confidence interval and 'P' value in the present study.
- In this study, 70 subjects who were undergoing tuberculosis treatment were enrolled. Treatment outcomes and safety parameters were assessed in the enrolled patients.
- Total no of patients enrolled in the study = 70

Gender distribution in Tuberculosis patients

Out of 70 tubercular patients enrolled in the study, 75.7% were males and 24.3% were females. Males are predominantly prone to tuberculosis than females.

Table 1: Distribution of patients based on Gender

S. No	Sex	No of patients (%)
1	Males	53(75.7%)
2	Females	17(24.3%)

Age wise distribution in tuberculosis patients

Patients in between 50–59 years age group are having higher incidence rate, followed by 30–39 years compared to other age groups. 10–19 years age group patients are recorded to have lowest incidence rate.

Social History: Out of 70 patients, TB was recorded mostly in alcoholics with 55.71%, followed by smokers with 27.14 %. Low effect was seen in tobacco chewers with 4.28%

Medical History

Out of 70 patients 3 patients (4.28%) were suffering from diabetes

Family History

Out of 70 patients in the study, 3 patients (4.28%) have family history of tuberculosis and 1 patient (1.43%)

Type of TB

Out of 70, all patients recruited were of pulmonary tuberculosis and no extra pulmonary tuberculosis patient was identified. Out of 70 patients in the study, 31(44.28%) patients were newly diagnosed with tuberculosis, 11(15.71%) patients had already completed tuberculosis treatment and 28(40%) patients discontinued their treatment due to various reasons.

Type of DOTS

Out of 70 patients enrolled in the study, 25(35.71%) patients were undergone CAT 1 treatment, 27(38.57%) patients were undergone CAT 2 treatment and 18(25.71%) patients were undergone MDR treatment.

Incomplete Course Reasons in 28 Patients

Out of 70 patients, 28 patients were under tuberculosis treatment but didn't complete the course due to following reasons: 4 patients had interruptions recorded, 20 patients discontinued the treatment and 4 patients have withdrawn the treatment due to resistance or sensitivity to drugs.

Adverse Drug Reactions

In 70 patients, 114 adverse drug reactions were seen, in which vomiting recorded highest percentage followed by as given table no: 7

Hematological and Biochemical Toxicities

Table 2: Distribution of patients based on age group

Age	10-19 yrs	20-29 yrs	30-39 yrs	40-49 yrs	50-59 yrs	60-70 yrs
Number	1	12	15	14	18	10
Percentage	1.42%	17.14%	21.42%	20%	25.71%	14.28%

Table 3: Distribution of patients based on social history

Parameters	Smokers	Alcoholics	Decreased Appetite	Tobacco Chewers
No of patients (%)	19(27.14%)	39(55.71%)	22(31.42%)	3(4.28%)

Table 4: Distribution of patients based on previous TB course

Previous Course	Newly Diagnosed	Completed	Defaulted
No of patients (%)	31(44.28%)	11(15.71%)	28(40%)

Table 5: Distribution of patients based on treatment

DOTS	CAT1	CAT 2	MDR
No of patients (%)	25(35.71%)	27(38.57%)	18(25.71%)

Table 6: Distribution of patients based on incomplete courses

Reasons	Interruptions	Discontinued	Withdrawal
No of patients (%)	4(14.28%)	20(71.42%)	4(14.28%)

Table 7: Percentage of patients with different Adverse Drug Reactions

S. No	ADRs	No of patients (%)
1	Vomiting	35 (30.70%)
2	Hepatitis	4 (3.50%)
3	Dermatitis	12 (10.52%)
4	Nausea	6 (5.26%)
5	Abdominal pain	16 (14.03%)
6	Giddiness	14 (12.28%)
7	Blurred vision	2 (1.75%)
8	Hearing disturbances	5 (4.38%)
9	Seizures	1 (0.87%)
10	Psychosis	1 (0.87%)
11	Peripheral neuropathy	5 (4.38%)
12	Arthritis	8 (7.01%)
13	Anemia	1 (0.87%)
14	Generalized weakness	3 (2.63%)
15	Insomnia	1 (0.87%)

Table 8: Hematological toxicities in the all recruited patients

S. No	Parameters	Mean ± SD
1	Haemoglobin	9.43095 ± 1.905
2	Total WBC	9985.29412 ± 2839.45496
3	RBC	3.23235 ± 0.79343
4	ESR	32.25806 ± 19.72472

Table 9: Biochemical toxicities in all recruited patients

Parameters	Before Treatment (Mean ± SD)	After Treatment (Mean ± SD)
SGOT	12.47143 ± 15.24079	22.44286 ± 13.52468
SGPT	17.05714±15.28273	24.48857±15.56814
Serum Creatinine	0.77857±0.1895	0.99143±0.20553
Uric Acid	3.054 ± 0.8605	4.21929± 0.93194

Table 10: SGOT levels before and after treatment in recruited patients

Category	Before treatment	After treatment
Category 1	12.38462±8.03484	19.23077±13.14186
Category 2	17.21714±18.51209	23.77143±16.78074

Note: CAT 1 before VS CAT 1 after (*p< 0.5 is considered significant) CAT 2 before VS CAT 2 after (* p< 0.5 is considered significant)

Table 11: SGPT levels before and after treatment in recruited patients

Category	Before treatment	After treatment
Category 1	14.48718±12.29221	23.23077±13.96511
Category 2	18.17429±14.05823	25.54857±16.5406

Note: CAT 1 before VS CAT 1 (** p< 0.05 is considered to be significant), CAT 2 before VS CAT 2 after (** p< 0.05 is considered to be significant)

Table 12: Serum creatinine levels before and after treatment in recruited patients

Category	Before treatment	After treatment
Category 1	0.8641±0.24223	1.1641±0.66272
Category 2	0.78571±0.25569	1.00829±0.33032

CAT 2 before vs CAT 2 after (** p< 0.05 is considered to be significant) and CAT 1 before vs CAT 1 after (*** p< 0.01 is considered to be significant)

Table 13: Uric acid levels before and after treatment in recruited patients

Category	Before treatment	After treatment
Category 1	3.43333±1.05913	4.30769±1.01057
Category 2	3.97714±1.02673	4.90457±1.24892

CAT 1 before vs CAT 1 after (*** p< 0.01 is considered to be significant),
CAT 2 before vs CAT 2 after (*** p< 0.01 is considered to be significant)

Table 14: Distribution of patients based on clinical outcomes

Outcomes	Improved	Unimproved	Death
No of patients (%)	37(52.85%)	33(47.14%)	0(0%)

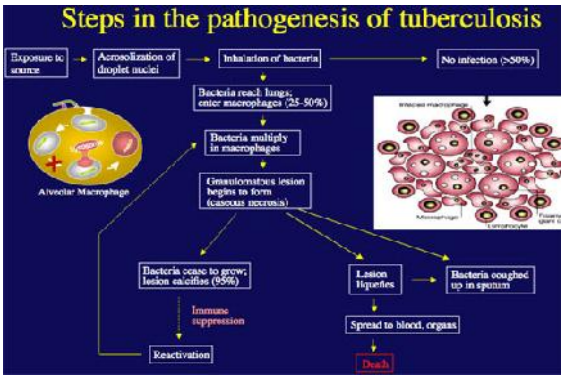


Figure 1: Steps in the pathogenesis of Tuberculosis

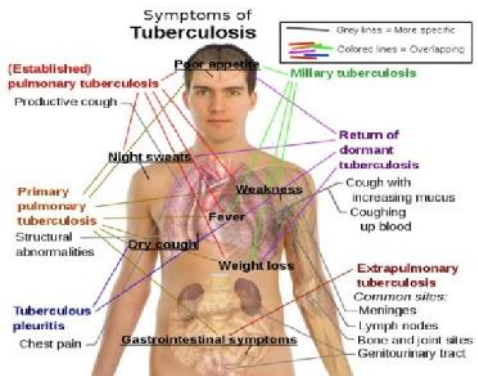


Figure 2: Symptoms of Tuberculosis

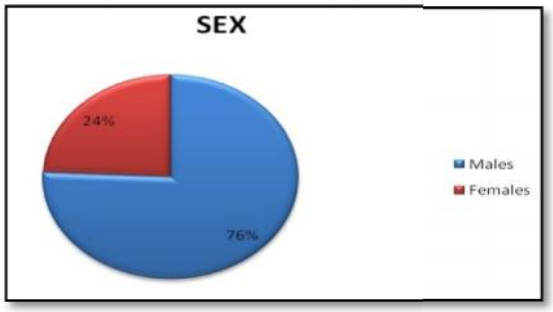


Figure 3: Distribution of patients based on gender

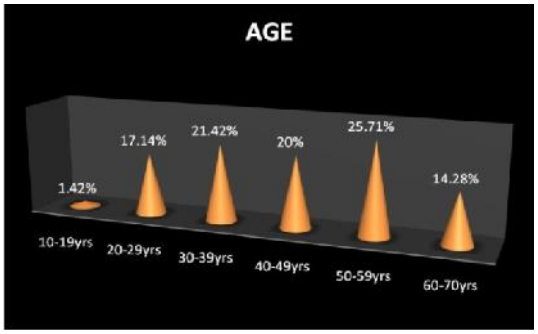


Figure 4: Distribution of patients based on age group

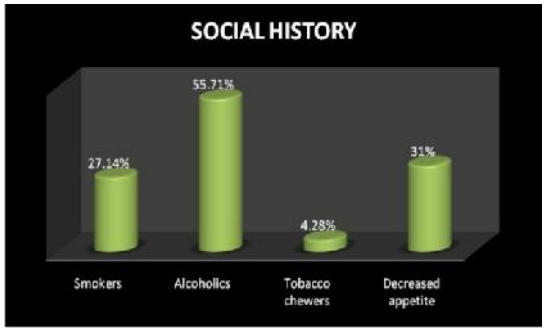


Figure 5: Distribution of patients based on social history

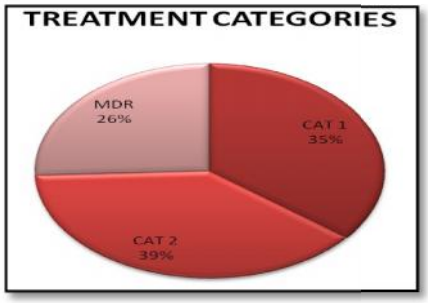


Figure 6: Distribution of patients based on treatment

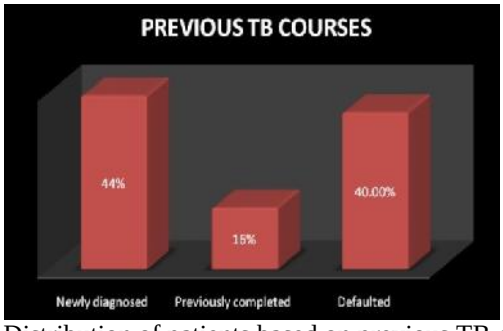


Fig 7: Distribution of patients based on previous TB course

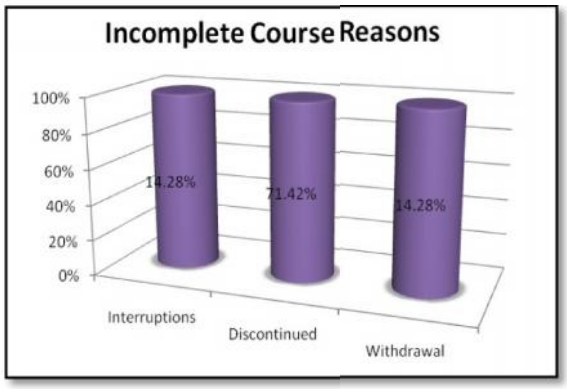


Figure 8: Distribution of patients based on incomplete courses

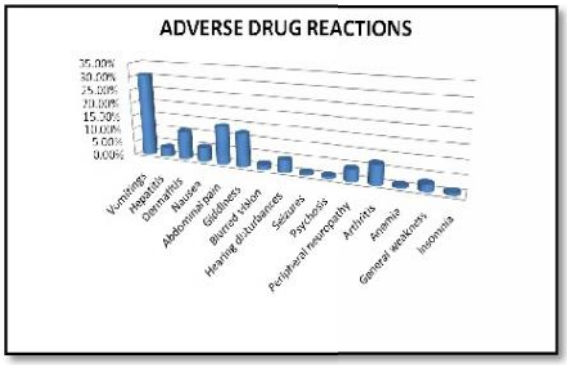


Figure 9: Distribution of patients based on adverse drug reactions

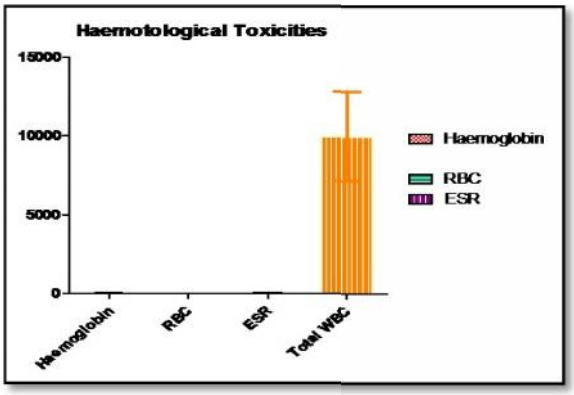


Figure 10: Bar graph showing hematological toxicities in all recruited patients

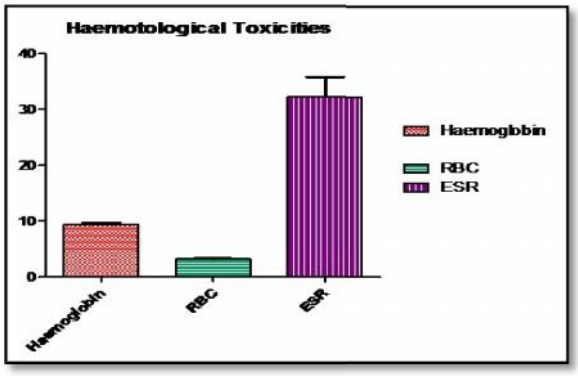


Figure 11: Bar graph showing Biochemical toxicities in all recruited patients

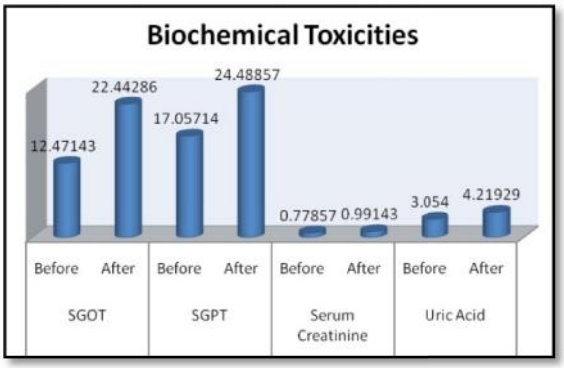


Figure 12: Bar graph showing mean of biochemical toxicities in all recruited patients

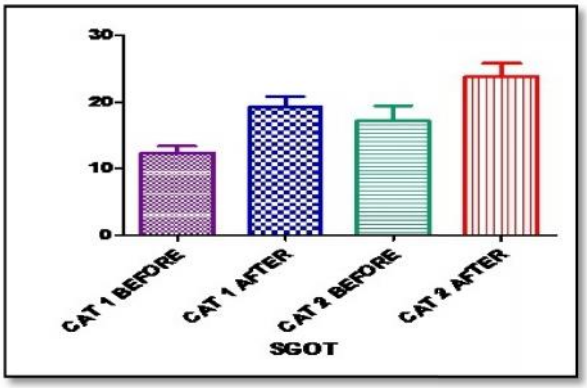


Figure 13: Bar graph showing significant increase in SGOT levels after treatment in CAT 1 and CAT 2 patients

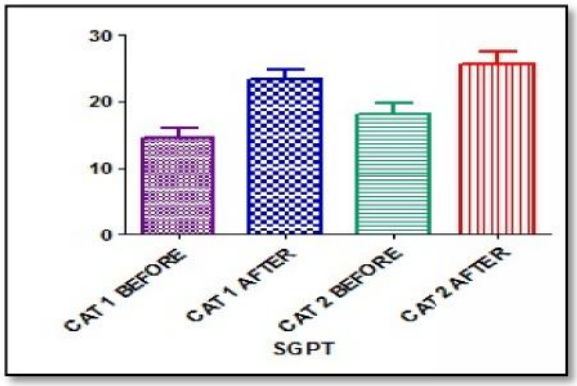


Figure 14: Bar graph showing significant increase in SGPT levels after treatment in CAT 1 and CAT

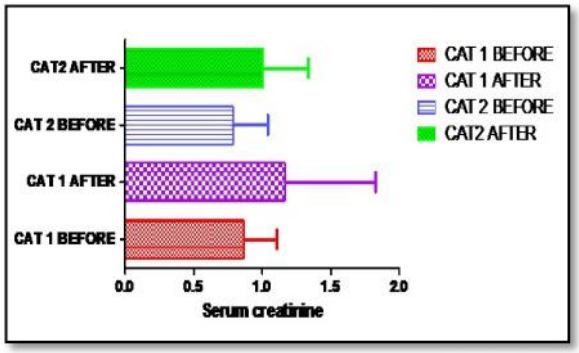


Figure 15: Bar graph showing significant increase in serum creatinine levels after treatment in CAT 1 and CAT 2 patients

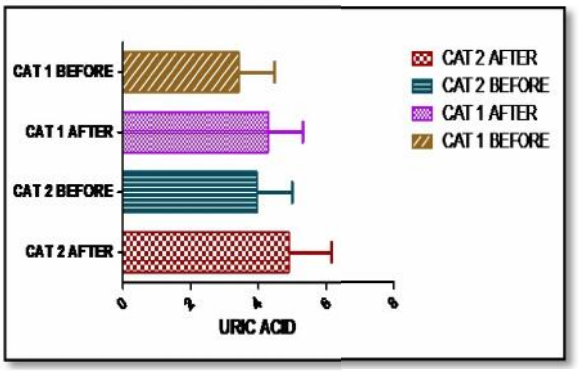


Figure 16: Bar graph showing significant increase in uric acid levels after treatment in CAT 1 and CAT 2 patients

Figure 17: Distribution of patients based on clinical outcomes

4. Discussion and Conclusion

Tuberculosis which had high rate of mortality need better understandings about the demographics, Socioeconomics, Family and Social history, treatment courses and risk factors for the development of the infection or for the worsening from better treatment outcomes. People of age above 30 years are at high risk to be affected by tuberculosis which is in accordance with many studies done globally and also in South Indian population [15]. It was proved in the study that male sex are mostly prone to the development of infection than female and the reason for this is still ambiguous to consider whether the socioeconomic factor or social habits like alcohol consumption, smoking and/or smokeless tobacco use and working environment may provoke them to the exposure of tuberculosis which can be turned out to be true form our study where patients with habits of alcohol consumption are high of 56% followed by smokers 27% and tobacco chewing of 4.23% [16-18].

Our results depicted 44% of newly diagnosed and 40% of defaulted patients. The reasons for course default are illiteracy, development of adverse drug reactions, employment. Our study showed that 71.4% of them defaulted because of discontinuation of the DOTS treatment, reason for this was known through patient counseling i.e. patients was not aware of the treatment course and their outcomes by incompletion of course, 14% of them defaulted because of interruptions due to development of adverse drug reactions like vomiting,

abdominal pain, dermatitis and the results of our study were in cordinance with study conducted by K. Jaggara jamma and co. in South India[19] and also because of lack of remembrance, work busy, functions, travelling etc. [20] 14% of them were withdrawn from treatment. A total of 120 patients were enrolled in the study out of which 70(58.3%) patients developed one or more adverse drug reactions which was found to be higher than the study conducted by Xiaozhen Lv and Anupa Khatri Chhetri in China and western Nepal. [21,22]

It was found that gastric system was involved at high percentage of 41% in development of adverse drug reactions followed by vestibular (15%) and musculoskeletal system (13%) where the results were corresponding to the study by Glauciene Santana Damasceno on people of Brazil. [23] Other systems involved in the development of adverse drug reactions are Skin (14%), CNS (8.23%), Hepatic (4%), Ocular (2.35%), Blood and lymphatic system (1.14%) and the results of the systems involved were identical to that of the study done by Kheirollah GHOLAMI within hospitalized patients. [24] Adverse drug reaction caused by Rifampin was at high incidence of 26% followed by Isoniazid 22%, Pyrazinamide of 20%, Ethionamide and Streptomycin of 10.6%, Kanamycin of 5.88%, Ethambutol of 2.35%, Cycloserine and Levofloxacin of 1.17%, was differing slightly from the study conducted by Daphne Yee et al., which stated that adverse drug reactions caused by pyrazinamide was higher followed by Isoniazid and Rifampicin. [25]

During the period of 6 months of study the major and significant adverse effect of the anti-tubercular drug i.e., elevation of SGPT and SGOT from their normal values before and after treatment was detected and the mean values were found to be as 28 and 36, 32 and 40. This condition proved sub clinical hepatitis. The blood sample were collected before and after 4 weeks after initiation of therapy as the time required for the complete elimination of the drug from the body was proved in various literatures to be 4 weeks. This significant elevation might be due to the reason of high number fast acetylators of isoniazide in the study than slow acetylators and due to potent enzyme inducing capacity of Rifampicin. The extent of elevation also depends on the alcohol consumption, severity of disease and nutritional status. The results were found to similar to the studies conducted at various places. [26-28] Our study gave out the results of high number of cat2 and MDR patients of 39% and 26% which include drugs Streptomycin which have a common side effect of nephrotoxicity.

Nephrotoxicity can be assessed by the measurement of serum creatinine levels before and after 4 weeks of the initiation of the therapy and difference of the mean values of creatinine before initiation and after 4 weeks of initiation of therapy is determined. Mean values of creatinine before and after the therapy was found to be as 0.9 and 1.2 which was found to match with the study conducted by Sandor Klis on streptomycin in treating other disease condition which showed the development of nephrotoxicity within 4 weeks of the treatment of 9% in 41 patients. [29-31]

Pyrazinamide causes the interruption in the excretion of the uric acid through kidney tubules and thus uric acid gets deposited within the body and the accumulation of the uric acid crystals within the joints further leads to gout and causes an adverse event of joint pains. This condition can be reversed ether by de challenging the drug or by adding Para amino Salicylic acid for the symptomatic relief. Our studies reported the mean values before and after the treatment as 4 and 5 where para amino salicylic acid was added in all the cases due to well established reason of no much detectable negative effect on the renal system due to pyrazinamide induced hyperuricemia and results moved along with the studies conducted by Ghulam Akbar Solangi and co, J. Schneeweiss and co. [32-33] The risk of hyperuricemia increases if pyrazinamide is combined with Ethambutol which was in cordinance with the study conducted by B.K. Khanna. [34]. Our study also evaluated hematological toxicities which evaluated parameters of hemoglobin, Neutrophils and ESR and these depicted the development of anemia and the mean values was found to be of 9 gm%, slight Neutropenia was seen, and increase in ESR which might be due to bacterial infection was reported and this was similar to the study conducted by Pravat Kumar Thatoi in odisa. [35]

India has high incidence of Diabetes which supports the bacterial growth within the system so it is referred as risk factors for the development of tuberculosis. Our study shows 4.3% of the patients are with Diabetes a risk factor for acquiring tuberculosis and this condition was proved in various studies conducted elsewhere in India. [36] Maintaining the blood glucose levels within the normal range will have negative effect in support of tuberculosis which was found out to be true when the patients enrolled in our study maintained their glucose levels within the normal range and is also supported by various studies. [37,38]

A study conducted in Ethiopia reported that there is increase in the risk of acquiring tuberculosis infection up to 6% if they are in contact with active tuberculosis people in their vicinities which was in contrast with our studies which reported the incidence of 4.28%. Reason behind this might be due to awareness campaign conducted throughout the country by various government bodies on the spread of the disease. [39] Patient education play a major role in beneficial clinical outcome of therapy, this has been proved from our results which showed 53% of them improved from the condition and 47% of them were not up to the mark in the treatment outcome, this was due to negligence of the patients and domination of their illiteracy or due to financial drawback or due to interruptions or family problems.

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