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Original research article

Study of Pyrazinamide Induced Hyperuricemia in Patients Undergoing DOTS Therapy for Tuberculosis at Tertiary Health Centre, Jhalawar (Rajasthan)

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Abstract

Background: Tuberculosis remains a global health problem despite of available anti tubercular treatment (ATT). Frequent discontinuation from treatment is a major factor due to associated adverse effects of drugs.

Objective: Altered Serum Uric Acid (SUA) Levels due to potent ATT drug, Pyrazinamide is being given under NTEP.

Study Design: Cross – sectional study

Place and duration: Department of T.B. and Chest diseases, Jhalawar Medical College, Jhalawar (Rajasthan) from 1st July 2021 to 31st March 2022.

Methodology: 110 patients of Tuberculosis on ATT - DOTS with Pyrazinamide (PZA) were included in study. Their SUA levels were determined on 0, 4 and 8 weeks.

Results: In the Intensive Phase of DOTS, Pyrazinamide drug is included for two months (8 weeks). In our study the Serum Uric levels were significantly increased in 84.9 % of T.B. patients.

Conclusion: Pyrazinamide as important drug in NTEP is associated with increased Serum Uric acid levels. During I.P. phase of DOTS, close monitoring of patient for SUA is needed to prevent defaults (discontinuation) and sequelae like arthralgia.

Key Words: Tuberculosis**,** PZA, Serum Uric Acid, ATT, DOTS

Introduction

The COVID-19 pandemic has reversed years of progress in providing essential TB services and reducing TB disease burden. Global TB targets are mostly off-track, although there are some country and regional success stories. The most obvious impact is a large global drop in the number of people newly diagnosed with TB and reported. This fell from 7.1 million in 2019 to 5.8 million in 2020, an 18% decline back to the level of 2012 and far short of the approximately 10 million people who developed TB in 2020. Sixteen countries accounted for 93% of this reduction, with India, Indonesia and the Philippines the worst affected.

Provisional data up to June 2021 show ongoing shortfalls. Reduced access to TB diagnosis and treatment has resulted in an increase in TB deaths. Best estimates for 2020 are 1.3 million TB deaths among HIV-negative people (up from 1.2 million in 2019) and an additional 214 000 among HIV-positive people (up from 209 000 in 2019), with the combined total back to the level of 2017. Declines in TB incidence (the number of people developing TB each year) achieved in previous years have slowed almost to a halt.[1]

Despite of using DOTS Thrice weekly strategy, then daily dose regimen even with newer and very costly drugs like Bedaquiline, Delamanid etc., the global disease prevalence couldn't decline as per our expectations. The Covid -19 pandemic, association of HIV, MDR – TB and XDR – TB, accelerated the existed TB problem.[2,3,4]

Mycobacterium Tuberculosis is Microaerophilic bacilli hence Pulmonary TB occurs more than five times of EPTB. Most of EPTB patients are latent without any symptoms but about 10 per cent may progress to active TB and if untreated may lead to death..[5,6,7] Symptoms of PTB are cough, expectoration, shortness of breath and blood in sputum.[7] EPTB depend on the site of occurrence.[8] Thus TB patients present organ specific and common symptoms like Fever, loss of appetite, weight loss, tiredness and night sweats etc.

DOTS therapy under NTEP, using Standard – regimen is 2HREZ / 4HER as daily FDC (6 months duration). Review and revision leaded to many changes in diagnostic as well as treatment strategies of Pulmonary and Extra – Pulmonary TB.

FDC (Fixed Drug Combinations) are being used to avoid the risk of Drug - resistance due to Monotherapy in treatment of tuberculosis. Pyrazinamide is the important component of FDC because of its Bactericidal and Sterilizing effect, in acidic media on Mycobacterium Tuberculosis during active stage of disease.[9] It is given with Isoniazid, Ethambutol, and Rifampicin, in Intensive – phase (I.P.) of Standard drug regimen.[10,11,12]

PZA drug is metabolized in to its active form Pyrazinoic – Acid which is further Oxidized by Xanthine Oxidase. The drug in its normal doses reduces about 80 per cent renal excretion of Uric acid.[13 - 15] Increased SUA levels precipitate as Urate crystals and cause Arthralgia and Gout.

The study was planned to observe the effects of PZA on Serum Uric Acid levels in TB patients on PZA containing DOTS therapy.

Material and Methods:

110 patients from 1st July 2021 to 31st March 2022, coming to O.P.D.. / Indoor of TB & Chest department of Jhalawar Medical College, were included in the present study. All were newly diagnosed patients of Pulmonary and Extra - Pulmonary Tuberculosis. They were given

PZA in the form of FDC for 08 weeks according to WHO recommendations.[16] Selection Criteria to include or exclude the patients were as follows:-

Inclusion Criteria –
1. Patients > 18 years of age.
2. Newly diagnosed as pulmonary or extra pulmonary TB patients

Exclusion Criteria –
1. Patients < 18 years of age.
2. Patients of tuberculosis with Arthralgia, Gout and other co-morbidities.
3. On ATT with PZA sparing regime.
4. Patients with deranged Renal and Hepatic function.

Serum Uric Acid levels at 0, 4th and 8th week of starting ATT were determined.
All participants were explained about study objectives and their role too. The Informed Consent was also taken before including them. SPSS 22.0 version was used to perform Statistical Analysis. Chi Square test was applied before and after start of PZA containing regime for determining gender difference in Serum Uric Acid levels of study samples. P value less than 0.05 was statistically significant in the study.

Results:

Table 1: is showing Age and Sex wise distribution of TB patients.

Age in Years	Males	Females	Total
18 - 30	04	01	05
31 - 40	26	15	41
41 - 50	32	21	53
51 - 60	04	03	07
61 - 70	02	01	03
71 - 80	01	00	01
Total	69	41	110

Out of 110 TB patients, 69 males and 41 females have participated in the study.
Hence 62.70 percent Males and 37.3 percent Females on PZA therapy were included to evaluate SUA levels.

Table 2: Distributions of Pulmonary TB and Extra-Pulmonary TB.

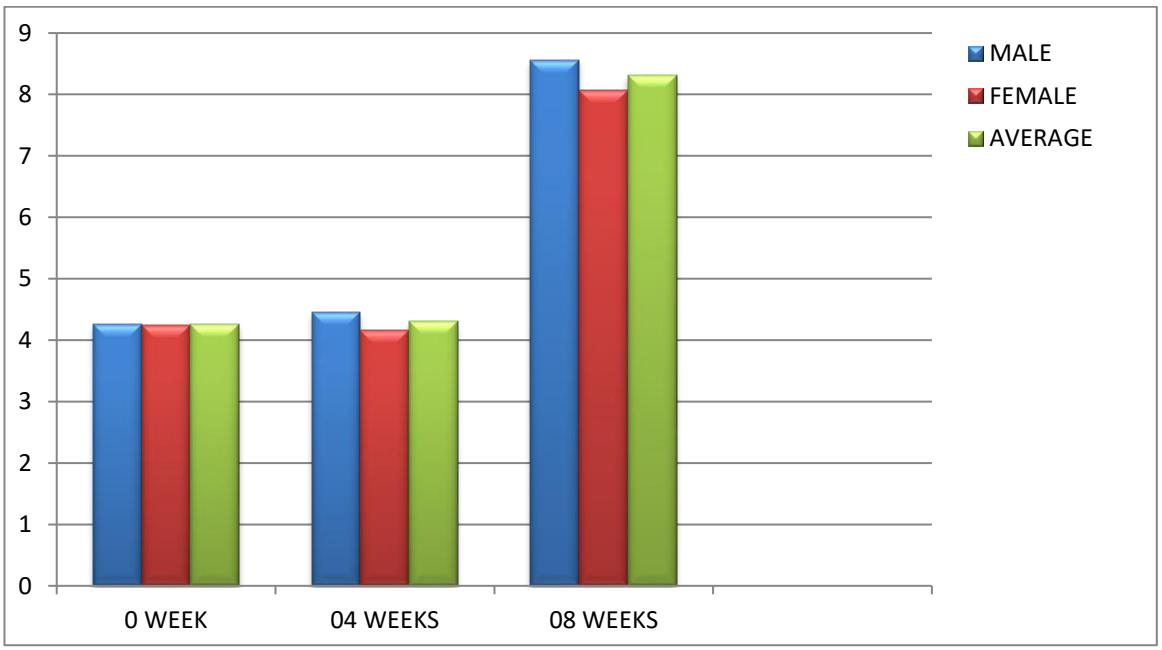
Type of Disease/Gender	Pulmonary Tuberculosis	Extra-Pulmonary Tuberculosis	Total
Males	55	14	69
Females	33	08	41
Total	88	22	110

Table 3: Shows SUA levels at 0, 04th, 08th weeks and P – values

S.U.A. Lavels	0 week	04 Weeks	08 Weeks
Males	4.25±0.73	4.45±0.51	8.56±1.78
Females	4.24±0.50	4.16±0.52	8.06±1.55
P - value	0.892	0.034	0.0145

Table 4: Shows Mean Difference of SUA levels after end of 8 Weeks

Serum Uric Acid levels (mg / dl)	Pre Treatment	Post Treatment	P - Value
	4.25±0.68	8.31±1.60	< .05



Graph 1: Serum Uric Acid Levels (mg/dl) at follow-up visits during treatment with PZA

Discussion:

Being as chronicity of disease, limited available ATD (Anti Tubercular Drugs) and despite of best revisions to control / eliminate tuberculosis, still we couldn't get the success. PZA is potent Intracellular Bactericidal drug used in standard regimen of DOTS for initial (I.P.) 2 months (8 weeks).[17] Due to increased SUA levels, the complaints of Arthralgia, warrant the patient to stop / discontinue ATT leading the outcome as Defaulter.

In our present study we observed increase in Serum Uric Acid level from 4.26 mg / dl, at the start of treatment (0 week) from 4.25 mg/dl to 8.31 mg/dl, at the end of I.P. (08 weeks). About 85 percent patients had reported increased SUA levels in this study. That were consistent to other similar studies done in the past.[18,19]

Sharma et al had shown hyperuricemia in 43.4 percent of T.B. patients of the study.[20] Horsfall et al also reported 51.6 percent patients on Pyrazinamide developed Hyperuricemia and 20 percent of them also reported Arthralgia which was reversed soon after stopping PZA.[21] Gender disparities of hyperuricemia were also evaluated by some studies.[22,23] Pokam et al reported higher Serum Uric Acid levels among males than in females.[24]

WHO reports that Tuberculosis two times more common in males. and Female ratio is 2 : 1, for which one of the causative important factor is lack of Medical accessibility.[25]
To know the effect of PZA to cause hyperurecmia was attempted among T.B. patients diagnosed and treated at tertiary health Centre, Jhalawar (Rajasthan) There was limitation to monitor the effects of individual drug due to FDC in NTEP.

Conclusion:

The Pyrazinamide is very important drug to treat communicable disease, Tuberculosis. It induces hyperuricemia which further increases the risk of Arthralgia and Gout. Hence it is highly mandatory to monitor SUA levels of all T.B. patients on PZA containing ATT to prevent frequent defaults.

Conflict of interest: Nil

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