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ORIGINAL ARTICLE

Pyrazinamide Induced Hyperuricemia in the Induction Phase of Anti-Tuberculosis Therapy

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ABSTRACT

Background: Tuberculosis (TB) is a global public health concern; although there are several recognized anti-tuberculosis drugs (ATDs) that effectively combat Mycobacterium tuberculosis (MTB), the associated adverse effects lead to frequent discontinuation.

Objective: To assess the metabolic disturbances resulting from Pyrazinamide, the altered serum uric acid (SUA) levels among TB patients in District Bunir.

Study Design: Cross-sectional study

Place and Duration of Study: Department of Medicine, Bilal Medical Trust Hospital, Bunir-KPK from 1st January to 30th September 2019.

Methodology: One hundred and nine tuberculosis patients were included in the study. All these patients were on ATD with Pyrazinamide and were regularly followed up, and their SUA levels were determined at weeks 0, 4 and 8.

Results: The serum uric acid levels were high in almost 85.3% in the intensive phase of anit-TB Therapy (ATT). Among female TB patients, the incidence rate of hyperuricemia was comparatively higher than males (88.1% vs. 81.0%), but there were no significant gender disparities.

Conclusion: The anti-tuberculosis drug with pyrazinamide is associated with an increased risk of hyperuricemia. Therefore, the illness needs to be closely monitored during the intensive phase of therapy.

Key words: Pyrazinamide, Tuberculosis, Hyperuricaemia

INTRODUCTION

Tuberculosis is a contagious infectious disease; spreads from person to person. It has been included among the ten leading causes of death worldwide as per the report published by World Health Organization (WHO). The fatality and TB-associated morbidity has also increased as compared to other infectious agents; it is now considered the leading cause of death from a single infectious agent, second to human immunodeficiency viruses (HIV). This curable infectious condition impacted around 10 million people in the year 2019, with increased incidences among males than females, leading to 1.4 million deaths.[1]

Although with DOTS strategy (directly observed treatment, short-course), the global disease prevalence has declined, but it remains a major health concern. Countries like Pakistan, Indonesia, Philippines, Nigeria, Bangladesh and South Africa contribute 2/3rd of the existing disease crisis.[1] According to the Global TB report, 562,000 Pakistanis developed TB in 2018, whereas only 369,548 cases were documented. However, the latter never received any treatment and possibly transmitted the infection to others.[2] Furthermore, the misdiagnosis and inaccurate decisions in TB management increase the overall TB-associated death, as it develops multi-drug resistance (MDR) in pathogen strains.[3,4] Hence, due to low treatment adherence, Pakistan has been the 5th highest contributor to the overall TB burden.[5,6] But this could be higher, as we have high underreporting rate.

Tuberculosis could be pulmonary or extrapulmonary, affecting other parts of the body. Most of the infections are latent, having no symptoms, but 10% of them progress to active TB and ultimately leading to death, if left untreated.[7]. Extrapulmonary TB can cause a wide range of symptoms[8], depending on the site of occurrence. However, some of the classic symptoms of active TB are fever, night sweats, chronic cough with blood-containing mucus and weight loss.[7]

WHO and the International Union against Tuberculosis and Lung Disease (IUATLD) recommend the treatment with fixed-dose combination (FDC) drugs as it obviates the risk of drug-resistant tuberculosis resulting from monotherapy. Pyrazinamide is an important first-line anti-TB drug; it is bactericidal and has a potent sterilizing effect principally in the macrophages acidic medium and at the inflammatory site.[9]. It is mostly used in combination with other drugs such as Isoniazid and Rifampicin.[10,11] Pyrazinamide effectively reduces the treatment duration and is hence used in the first two months.[12] Though with effective therapeutic outcomes, Pyrazinamide is known to increase urate production and subsequently leads to hyperuricemia by inhibiting the secretion of uric acid from renal tubules.[13-15]

There is ample data regarding TB prevalence both nationally and internationally. But we locally lack data regarding the safety and efficacy of ATT. Therefore, through this research, we aimed to observe the effect of Pyrazinamide on SUA levels among TB patients.

MATERIALS AND METHODS

This cross-sectional study was conducted at the OPD of Bilal Medical Trust Hospital, Bunir, from 1st January to 30th September 2019. A total of 109 patients with disease symptoms, i.e. chest pain, coughing, night sweat, and already diagnosed TB were included in the study. While non-consenting patients, those who had contraindications and even those who were having complex infectious conditions were excluded. All of the enrolled patients were treated with Pyrazinamide for 8 weeks according to the

recommendations of WHO[16]. The patient's data, including demographics and clinical characteristics, were obtained and recorded using a structured questionnaire. All of the enrolled subjects were regularly followed up, and their SUA levels were determined at weeks 0, 4 and 8. The patients were well informed regarding the study objective and only included after obtaining written informed consent. The statistical analysis was performed using SPSS version 22.0. Chi-square test was applied to determine the gender-based difference in the SUA levels of the study sample before and after treatment with Pyrazinamide, and a p-value less than 0.05 was considered statistically significant.

RESULTS

There were 61.5% were females and mean age was 39.91±19.92 years (Table 1). Table 2 shows the mean difference in SUA levels among the patients after 8 weeks of the treatment with Pyrazinamide. There was a significant mean difference in the mean uric acid at week 0 and week 8 ($p<0.05$).

The mean SUA levels remained stable from week 0 to week 4, where a very slight change was observed. But it significantly increased by the end of intensive phase therapy (week 8). The mean SUA levels increase from week 0 to 8 in both genders, but there were no significant gender-based differences in week 0 and week 8. While males showed a significantly higher mean SUA in week 4 than females ($p=0.013$).

Table 1: Baseline characteristics of subjects

Variable	No.	%
Age (years)	39.91±19.92	
Gender		
Female	67	61.5
Male	42	38.5
Type of TB		
Extrapulmonary	20)	18.3
Pulmonary	89	81.7

Table 2: Mean Difference in SUA levels after 8 weeks of treatment

SUA levels (mg/dl)	Pre-treatment (week 0)	Post-treatment (week 8)	P value
	4.25±0.69	8.26±1.62	<0.05

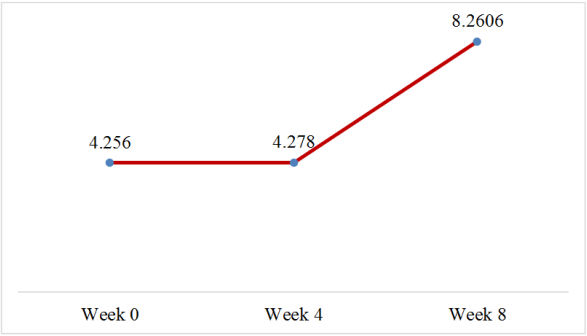

Fig. 1: Serum Uric Acid levels (mg/dl) at follow-up visit during treatment with Pyrazinamide

Table 3: Gender-wise variation in the mean SUA levels

SUA Levels (mg/dl)		Gender		P value
		Male	Female	
Pre-treatment	Week 0	4.24±0.75	4.26±0.65	0.899
Post-treatment	Week 4	4.43±0.48	4.18±0.50	0.013*
	Week 8	8.54±1.74	8.08±1.53	0.145

DISCUSSION

Tuberculosis is a communicable disease; therefore, the therapeutic measures are focused on complete bacterial eradication. The use of Pyrazinamide in the intensive phase of the disease is critical but has been known to improve sputum conversion rate. The therapeutic outcomes are entirely dependent on the patient's ATT tolerance and treatment compliance. Pyrazinamide, isoniazid, rifampicin, ethambutol or streptomycin are the four known therapeutic agents used for TB treatment[17]. These drugs' safety and efficacy profile have not been thoroughly evaluated, but the Pyrazinamide and ethambutol have known to affect the SUA levels resulting in hyperurecemia.[17]

In the present study, we observed an increasing trend in the SUA levels from 4.25±0.69 mg/dl at week 0 (baseline) to 8.26±1.62 at week 8 (after two months of therapy) (Table 2 & Fig. 1). Around 88.1% of our patients were diagnosed with hyperuricemia by the end of week 8. These findings were consistent with other studies.[18,19] A local study from Jamshoro reported a baseline SUA level of 2.6 mg/dl and 7.2 mg/dl at week 8 in association with Pyrazinamide use.[19] Similarly, Sharma et al[20] showed hyperuricemia among 43.4% of the enrolled TB patients treated with Pyrazinamide, respectively. A Nigerian study reported that 51.6% of patients on similar ATD developed hyperuricemia, and 20% of them also suffered from joint pain; these side-effects resolved soon after discontinuation of ATT.[21]

Several studies evaluating gender disparities in TB treatment outcomes have been conducted.[22,23] The disease burden is higher among males than females; WHO reports twice as many TB incidences among males than females.[24] The financial dependence and lack of medical accessibility might be the reason for reduced rates among females. Pokam et al[25] also reported higher SUA levels among males than females. In contrast, more than 60% of the TB patients admitted during the study duration were female, so incidence of hyperuricemia was ultimately high among them but the side-effect also prevailed within the female gender (88.1%).

Although this research was the first attempt to identify the ATT effects among TB patients from district Bunir, Khyber Pakhtunkhwa, there were limitations of small size; we also didn't monitor the combination therapy effects. Large-scale studies investigating the effect of combination drugs are recommended to determine the safety and efficacy profile of each drug and drug in combination as well.

CONCLUSION

The Pyrazinamide induces hyperuricemia among TB patients in the intensive phase of the therapy, which further increases the risk of other serious illnesses like gout and kidney stones. Therefore, it is essential to monitor the disease concerning the treatment to effectively control the side effects.

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