Original Article

Assessment of Prognostic Significance of Haematological Parameters after the Intensive Phase Treatment in Patients of Pulmonary Tuberculosis

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ABSTRACT

Introduction: Drug-induced hematologic disorders cover nearly the entire spectrum of haematology and can affect red blood cells, white blood cells, platelets, and the coagulation system. Widespread drug-induced haematological syndromes are mediated by various pathways, including immune effects, interactions with enzymatic signalling pathways, and direct inhibition of haematopoiesis. Various reports have shown that hematopoietic changes occur in tuberculosis patients. Hematologic adjustment associated with tuberculosis treatment has been disclosed from many parts of the world.

Aims/ objective: To determine the effects of anti-tubercular drugs on the hematologic profile of tuberculosis patients. In this study, we evaluated patients' haematological findings before and after the intensive phase of anti-tubercular pharmacotherapy.

Materials and Method: Approximately 5 ml of venous blood was aseptically collected using EDTA tubes from each of the study participants. Blood samples were taken from each study subject before starting treatment with anti-tubercular pharmacotherapy and after completing 2 months of intensive phase pharmacotherapy. Haematological profiles were evaluated using an automated haematology analyser. We used paired t-tests to compare hematologic values before and after the intensive phase of tuberculosis treatment. P-values less than 0.05 were considered as statistically significant.

Results: There was significant increase in haemoglobin and red cell distribution width (RDW) whereas there was significant fall in packed cell volume (PCV) and platelet cell distribution width (PDW) after intensive phase of anti-tubercular pharmacotherapy ($p<0.05$). There was appreciable decrease in neutrophils and platelets after intensive phase of anti-tubercular pharmacotherapy but this decrease was not statistically significant.

Conclusion: The variety of haematological abnormalities seen in patients of pulmonary tuberculosis after intensive phase anti-tubercular pharmacotherapy suggest the requirement for continuous monitoring and assessment of patients suffering from tuberculosis for adverse changes in haematological parameters during anti-tubercular pharmacotherapy.

Keywords: Pulmonary Tuberculosis, Intensive Phase, Anti-tubercular Drugs, Haematological Parameters.

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INTRODUCTION

Tuberculosis (TB) is a chronic disease caused by Mycobacterium tuberculosis (MTB) and is the most frequent infectious disease today. In 2018, there will be approximately 10 million new cases worldwide and 1.6 million deaths per year. [1, 2] Tuberculosis has surpassed HIV/AIDS and is also one of the leading causes of death.[3] Additionally, an estimated 2.5 billion people have latent tuberculosis. [4, 5]

Tuberculosis has been recognized as a major public health concern over the last 30 years. There is only a slight decrease of 2% per year globally despite the worldwide adoption of short courses of directly observed therapy (DOTS). [6-8]

Newly diagnosed tuberculosis patients worldwide received a standard first-line treatment regimen (2HRZE/4HR) consisting of four antibiotics, isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E). It is treated with 2-month initial intensive phase (2RHZE) then 4-month continuation phase (4RH) is given to patients. [9, 10]

Bacteriological status, sputum smear microscopy (SSM) conversion, and/or sputum culture conversion (SCC) at 2 months are used to monitor tuberculosis treatment outcomes every 2 months during the intensive and maintenance phases. It is commonly used as a microbiological milestone].[11-12] Failure to convert these two biomarkers of treatment prognosis was associated with unfavourable outcomes and increased treatment failure rates, including drug resistance and relapse.[13] Sensitivity for switch to negative sputum culture after 2 months of anti-tuberculosis treatment is only 40%, and although the SSM has little sensitivity and specificity to

detect errors, no other tuberculosis biomarker meets this level of qualification. [14]

Haematological disorders emerge from a variety of pathways and etiologies. Drug-induced hematologic disorders cover nearly the all spectrum of haematology and can affect red blood cells, white blood cells, platelets, and the coagulation system. Widespread drug-induced haematological syndromes are mediated by various pathways, including immune effects, interactions with enzymatic signalling pathways, and direct inhibition of haematopoiesis. Drug-induced syndromes consist of haemolytic anaemia, erythropoiesis, sideroblastic anaemia, megaloblastic anaemia, polycythaemia, aplastic anaemia, and leucocytosis. There are four imaginable relationships between tuberculosis and blood disorders. These are blood diseases that predispose to reactivation of tuberculosis. Drugs can cause idiosyncratic reactions, malabsorption, impaired iron metabolism and haemolysis in patients with red blood cell enzyme deficiency. Idiosyncratic reactions, manifested by inhibition of one or all of the three components of blood cells (leukocytes, erythrocytes, platelets) along with the coagulation system, can be induced by any of the anti-tubercular pharmacotherapy. [15, 16]

The extent of drug-induced Haematological abnormalities has been studied in various parts of the world. For example, leukopenia after rifampicin and isoniazid therapy has been recorded in Japan.[17] Anti-tubercular drug-induced normocytic-normochromic anaemia is the most frequent abnormality observed in Malaysia.[18] Studies have reported anaemia prevalence of 74% and leucocytosis of 26% and leucocytosis of 24% in India.[19] A study conducted in South Africa reported 15% leukopenia, 23% thrombocytopenia, and 87% lymphopenia as a result of anti-tubercular pharmacotherapy.[20] In another study conducted in Nigeria, hematologic abnormalities due to anti-tubercular pharmacotherapy were recorded in 93.6, 22.3, 45.2, and 4.8% for anaemia, leucocytosis, neutropenia, and lymphopenia, respectively.[21] In addition, 86% of anaemia due to anti-tubercular pharmacotherapy has been reported in Tanzania. [22]

Various reports have shown that hematopoietic changes occur in tuberculosis patients. Hematologic changes concurrent with tuberculosis treatment have been studied in numerous parts of the world. However, to our familiarity, there are no extensive studies examining hematologic abnormalities in tuberculosis patients in India. Therefore, this study was planned to determine the effect of anti-tubercular pharmacotherapy on the hematologic profile of tuberculosis patients. In this study, we assessed the hematologic findings of patients before and after the intensive phase of anti-tubercular pharmacotherapy.

MATERIALS AND METHODS

This was an observational and prospective study done in tertiary care centre of eastern India from August 2020 to July 2021. The study was anticipated to involve less than minimal risk to the patients, so exemption from ethics committee review was taken. Participant information sheet was provided and explained to the patients and then informed consent was taken.

Inclusion Criteria

Patients of age greater than 18 years of either gender visiting out-patient department of general medicine with the diagnosis of pulmonary tuberculosis by smear microscopy and MTB sputum culture. The diagnosis was confirmed by chest X-ray or chest Computer Tomography (CT).

Exclusion Criteria

Patients having extra-pulmonary tuberculosis or MDR or XDR tuberculosis, patients who have history of previous anti-tubercular pharmacotherapy, death during pharmacotherapy, patients having other infection, autoimmune disease, chronic inflammatory disease or any other diseases that can affect haematological parameters, Patients treated with steroids or any other immunosuppressant drugs.

To focus on more specific effects of tuberculosis treatment, we excluded patients with different comorbidities. This is because the various drugs taken by these patients can change Haematological parameters, and comorbidities can significantly reduce treatment success.

Sample size

Study participants were recruited using a time-limited continuous sampling technique. All newly diagnosed tuberculosis patients seeking anti-tubercular pharmacotherapy in a general practice clinic were included in this study. A total of 85 new tuberculosis patients were recruited and included in this study using the inclusion and exclusion criteria established for this study.

Socio-demographic characteristics like age, sex, marital status, and place of residence, and clinical information such as anorexia, weight loss, night sweats, and fever, were collected using pre-tested structured questionnaires. Socio-demographic characteristics of tuberculosis patients were collected by trained clinical nurses and laboratory technicians.

Approximately 5 ml of venous blood was aseptically collected using EDTA tubes from each of the study participants. Blood samples were taken from each study subject before starting treatment with anti-tubercular pharmacotherapy and after completing 2 months of intensive phase pharmacotherapy. Hematologic parameters like Red blood cell count, haemoglobin level, Packed Cell Volume (PCV), Red blood cell indices such as mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), total white blood cell count (WBC), WBC differential count, Platelet count, Red cell distribution

width (RDW), and platelet cell distribution width (PDW) were evaluated using an automated haematology analyser according to the Standard Operational Procedures (SOP) of the institute and manufacturers instruction.

Statistical Analysis

Data were reviewed, sorted, and designated manually using Microsoft Excel 365. Data were then shifted to the SPSS version 25 statistical package for analysis. Frequencies and cross tabulations were used to compile descriptive statistics. We used paired t-tests to compare hematologic values before and after the intensive phase of tuberculosis treatment. Chi-square test was used to compare proportion of patients with low, normal, or high value of parameters. P-values less than 0.05 were considered as statistically significant.

OBSERVATIONS AND RESULTS

Most of the patients in our study belonged to age group 31-45 years. There was male preponderance. Most of the patients belonged to lower middle socioeconomic status.

Table 1: Baseline Demographic and Clinical Characteristics (n = 85)

Variables	Value	Percentage
Age		
18-30	32	37.65
31-45	36	42.35
>45	17	20.00
Gender		
Male	49	57.65
Female	36	42.35
Residence		
Urban	40	47.06
Rural	45	52.94
Socioeconomic status [23]		
Upper	11	12.94
Upper middle	23	27.06
Lower middle	32	37.65
Upper lower	12	14.12
Lower	7	8.24

Table 2: Comparison of Haematological Profiles before and after Intensive Phase of Anti-tubercular Therapy (n = 80)

Variables	Before IP (Mean ± SD)	After IP (Mean ± SD)	P-Value (Paired t test)
Hb (g/dl)	11.65 ± 2.18	12.85 ± 1.76	**0.0002***
RBC/ µl	4.16 ± 0.94 x 10^6	4.37 ± 1.04 x 10^6	0.1822
PCV	38.61 ± 6.02	35.79 ± 4.39	**<0.0001***
Total leucocyte count / µl	(7.67 ± 3.38) x 10^3	(6.91 ± 3.87) x 10^3	0.1878
Neutrophils / µl	(4.83 ± 2.42) x 10^3	(4.11 ± 2.53) x 10^3	0.0677
Lymphocyte / µl	(1.74 ± 0.95) x 10^3	(2.03 ± 1.25) x 10^3	0.1005
Platelets / µl	(259.61 ± 97.84) x 10^3	(213.18 ± 113.29) x 10^3	0.0062
MCV (fl)	89.97 ± 6.72	91.23 ± 8.56	0.3020
MCH (pg)	30.24 ± 3.02	29.52 ± 4.51	0.2372
MCHC (g/dl)	30.31 ± 2.86	29.67 ± 3.98	0.2446
RDW	17.48 ± 1.43	26.98 ± 2.69	**<0.0001***
PDW	16.95 ± 1.14	15.23 ± 1.98	**<0.0001***

Hb: Haemoglobin, RBC: Red Blood Cell, PCV: Packed Cell Volume, MCV: Mean Corpuscular Volume, MCH: Mean Corpuscular Haemoglobin, MCHC: Mean Corpuscular Haemoglobin Concentration, RDW: Red Cell Distribution Width, PDW: Platelet Distribution Width.

µl: micro liter, fl: femto litter (10−15L), pg: pico-gram (10−12g), * significant association

There was significant increase in haemoglobin and RDW whereas there was significant fall in PCV and PDW. There was appreciable decrease in neutrophils and platelets but this decrease was not statistically significant.

Table 3: Proportion of Patients with Low, Normal and High Haematological Profile before and after Intensive Phase of Anti-tubercular Therapy (n = 80)

Variables	Category	Before IP (Mean ± SD)	After IP (Mean ± SD)	Reference Level	P-Value (Chi-Square Test)
Hb	High	3	2	Male: 13-17 g/dl Female: 12-15 g/dl	0.1187
	Low	47	60		
	Normal	35	23		
RBC	High	4	5	4.5 to 5.5 x 10^6 / µl	0.9143
	Low	45	46		
	Normal	36	34		
PCV	High	7	3	Male: 40-50 % Female: 36-46 %	**0.0164***
	Low	43	61		
	Normal	35	21		
Total leucocyte count	High	16	14	4-10 / µl	0.7884
	Low	12	15		
	Normal	57	56		
Neutrophils	High	10	11	2-7 / µl	0.2979
	Low	6	12		
	Normal	69	62		
Lymphocyte	High	2	4	1.5-4.5 / µl	0.6303
	Low	2	3		
	Normal	81	78		
Platelets	High	16	8	150-400 / µl	0.2093
	Low	11	13		
	Normal	58	64		
RDW	High	25	80	11.5-14.5 %	**<0.0001***
	Normal	60	5		
PDW	High	6	2	10-17 %	0.1474
	Normal	79	83		

Hb: Haemoglobin, RBC: Red Blood Cell, PCV: Packed Cell Volume, MCV: Mean Corpuscular Volume, MCH: Mean Corpuscular Haemoglobin, MCHC: Mean Corpuscular Haemoglobin Concentration, RDW: Red Cell Distribution Width, PDW: Platelet Distribution Width.
µl: micro liter, fl: femto litter (10−15L), pg: pico-gram (10−12g), * significant association

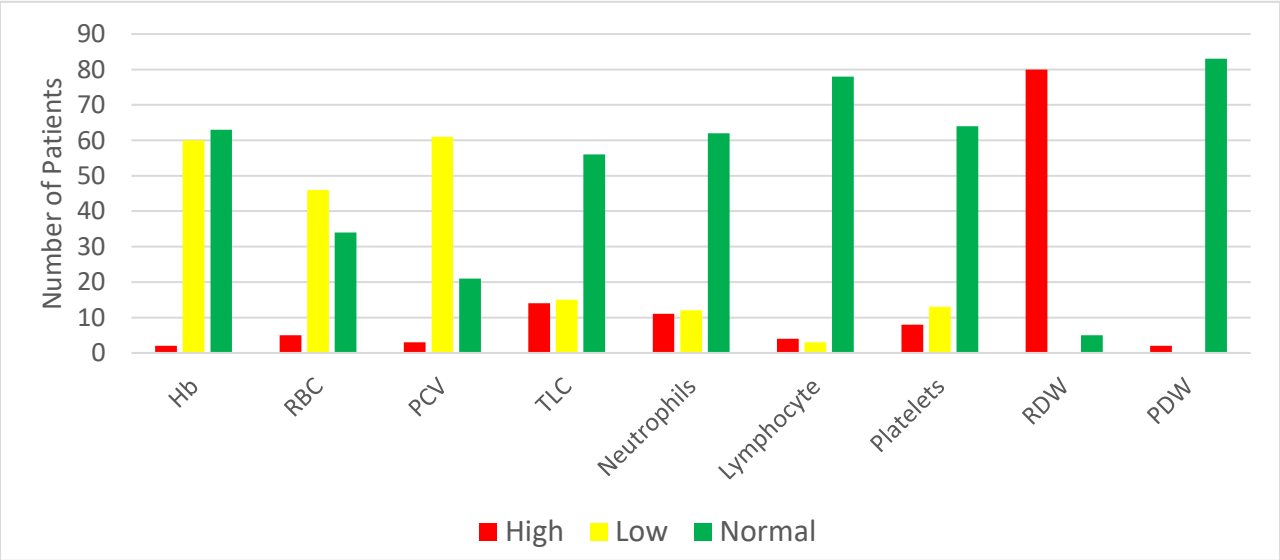

Figure 1: Proportion of Patients with Low, Normal and High Haematological Profile after Intensive Phase of Anti-tubercular Therapy

DISCUSSION

The present study compared the hematologic parameters of HIV-negative tuberculosis patients before starting treatment and after completing the intensive phase of anti-tubercular pharmacotherapy. In the present study, the mean RBC of a TB patient before starting anti-TB therapy was relatively equal to RBC after completing the intensive phase of anti-tubercular pharmacotherapy.

Haemoglobin concentrations and packed cell volume were somewhat higher in treatment-naïve tuberculosis patients than in those who received 2 months of anti-tubercular pharmacotherapy. However, the proportion of tuberculosis patients with low Haemoglobin and low haematocrit increased significantly after completing the intensive phase of anti-tubercular pharmacotherapy. All chronic infections, including tuberculosis, can cause anaemia.[24] Although various etiologies have been proposed for tuberculosis-related anaemia, most studies point to suppression of erythropoiesis by inflammatory mediators as the explanation of the anaemia.[25] Nutritional deficiencies and malabsorption syndromes can exacerbate the severity of anaemia.[26] Possible mechanisms for the progression of anaemia during tuberculosis infection may be nutritional deficiencies, impaired iron utilization, malabsorption, bone marrow granulomas, and shortened erythrocyte survival. [27]

Weiss, Means and Nemeth et al. commented on the mechanism that causes the pathogenesis of anaemia in patients of pulmonary tuberculosis. [24, 28, 29] They reported that that the bacterial infection causes activation of T-lymphocyte and macrophages, which leads to the formation of the cytokines like tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), Interlukin-1 (IL-1) and interlukin-6 (IL-6) which with their subsequent pathways will cause redistribution of iron into iron stores of the reticuloendothelial system leading to reduction in iron concentrations in the blood thus decreasing its availability to red cells for synthesis of haemoglobin, inhibition of proliferation of erythroid progenitor cell and defective production and activity of erythropoietin which may cause anaemia and decreased response of the bone marrow to anaemia respectively. The high incidence of decreased haemoglobin and haematocrit concentration in tuberculosis patients after completion of the intensive phase of anti-tubercular pharmacotherapy may suggest drug induced anaemia among patients of pulmonary tuberculosis. Drugs can cause various haematological disorders affecting red blood cells, white blood cells and platelets. Drug induced syndromes consist of haemolytic anaemia, sideroblastic anaemia, megaloblastic anaemia, polycythaemia, methaemoglobinemia, red cell aplasia, and aplastic anaemia.[15]

Total white blood cell counts in tuberculosis patients before starting anti-tubercular pharmacotherapy were relatively comparable to those after completing the intensive care phase. However, leucocytosis did not occur before patients started treatment nor after patients finished 2 months of treatment. In a study evaluating hematologic abnormalities in tuberculosis patients by Singh et al., 25% of leukopenia and 22% of neutropenia were found in tuberculosis patients.[30] Drug-induced neutropenia has also been disclosed in association with various analgesic, psychotropic, anticonvulsant, anti-thyroid, antihistamine, anti-rheumatic, gastrointestinal, antibiotic, and cardiovascular drugs. [31]

The results of this study reveal that platelet count is another important Haematological profile when comparing platelet counts before starting TB treatment with platelet counts after two months of anti-tubercular pharmacotherapy. Nearly half of tuberculosis patients who had high platelet counts before treatment had low platelet counts after completing the intensive care phase. This finding is backed by a report from India suggesting that the low platelet count may be due to platelet destruction by anti-TB drugs and the immune system.[32] The classic causes of drug-induced thrombocytopenia are quinine and quinine-like drugs.[33] Thrombocytopenia induced by these agents is nonresponsive in the absence of the drug, but antibodies that bind to epitopes on the platelet membrane, glycoproteins IIb/IIIa or Ib/IX, in the presence of sensitizers caused by Vancomycin may also be associated with marked thrombocytopenia and detectable serum drug-dependent antibodies.[34] Other drugs associated with thrombocytopenia include antibiotics (sulfonamides, rifampicin, linezolid), anti-inflammatory drugs, antineoplastic drugs, antidepressants, benzodiazepines, anticonvulsants (carbamazepine, phenytoin, valproic acid), and It includes cardiovascular drug and antihypertensive drugs as well. [35, 36]

There was significant increase in RDW after intensive phase of anti-tubercular pharmacotherapy while there was slight significant decrease in PDW. Red blood cell distribution width and PDW measure variations in red blood cell and platelet mass. RDW is used to diagnose anaemia. Domingo et al. reported that patients with higher RDW values had greater decreases in Haemoglobin concentration. [37] The width of the red blood cell distribution is often used to distinguish between single-cause and mixed-cause anaemia. Documented vitamin B12 or folic acid deficiency causes macrocytic anaemia (macrocytic anaemia), with an elevated RDW in about two-thirds of all cases.[38] However, since the different size distribution of erythrocytes is a hallmark of iron deficiency anaemia, virtually all cases show an increased RDW.[39] Long-term use of anti-tubercular drugs increases the risk of side effects and toxicity. Isoniazid and rifampicin can directly cause haemolytic anaemia, and pyrazinamide can cause sideroblastic anaemia.[40] Anaemia is part of the clinical manifestation of tuberculosis, and some believe it is due to the chronic disease. In general, tuberculosis patients are highly predisposed to gastrointestinal absorption problems, resulting in anaemia[26]. The presence of microcytic erythrocytes before treatment and the production of circulating normocytic erythrocytes after treatment cause high size variation (increased RDW values). Lee et al. showed that anaemia is a frequent hematologic abnormality in patients.[26] Bain et al.

stated that RDW values in chronic inflammatory diseases such as tuberculosis are analogous to those occurring in iron deficiency anaemia, consistent with current research. [25]

Platelet distribution width is a direct measure of platelet size variability and has been used to distinguish between platelet disorders such as essential thrombocythemia and reactive thrombocytosis.[41] In the current study, PDW in tuberculosis patients decreased significantly after taking anti-TB drugs for 2 months. Previously, Tozukoparan et al. disclosed that PDW value in a tuberculosis patient was significantly higher (40±23.5) and significantly decreased under anti-tubercular pharmacotherapy.[42] Thrombocytopenia is a serious adverse effect that can be caused by anti-tuberculosis drugs, mainly occurring with rifampicin (RIF). [43] The primary mechanism of thrombocytopenia is reduced production or elevated destruction of platelets. The drug non-covalently binds to membrane glycoproteins to generate composite epitopes or induce antibody-specific conformational changes. In addition, RIF-dependent antibodies adhere to platelets and increase their destruction.[44] However, the exact pathway of INH-induced thrombocythemia is unknown.

The results of this study showed that Haemoglobin concentration, PCV, platelet count, and PDW values decreased after completion of the intensive phase of anti-tubercular pharmacotherapy. This is due to the reason that iron is utilized for growth of Mycobacterium tuberculosis in macrophages leading to iron deficiency anaemia. After intensive treatment, the body has enough iron to form normal red blood cells. The findings of this study are supported by Tozukoparan et al., showing significantly lower PDW values under anti-tubercular pharmacotherapy.[42] Another study by Sahin et al. noted that reactive thrombocytosis and PDW often develop in patients with pulmonary tuberculosis. It is associated with acute phase reactants that reduce the post-treatment inflammatory response. [45]

CONCLUSION

The variety of haematological abnormalities seen in patients of pulmonary tuberculosis after intensive phase anti-tubercular pharmacotherapy suggest the requirement for continuous monitoring and assessment of patients suffering from tuberculosis for adverse changes in haematological parameters during anti-tubercular pharmacotherapy. Haemoglobin, haematocrit, and platelet count values in tuberculosis patients decreased significantly after completion of the intensive phase of anti-tubercular pharmacotherapy compared with corresponding values before initiation of anti-tubercular pharmacotherapy. Anaemia has been found to be one of the most common hematologic abnormalities seen in patients undergoing anti-tubercular pharmacotherapy. Therefore, anaemia and thrombocytopenia should be monitored regularly during tuberculosis treatment.

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