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STUDY OF HAEMATOLOGICAL PROFILE & CHANGES IN HAEMATOLOGICAL PROFILE CAUSED BY FIRST LINE ANTITUBERCULAR DRUGS IN PATIENTS WITH PULMONARY TUBERCULOSIS

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Abstract

Background: Newly diagnosed TB cases across the globe are treated, according to the latest World Health Organization (WHO) guidelines, with a standard first-line treatment regimen (2HRZE/4HRE) of four antibiotics, isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E). Present study was aimed to study haematological profile & changes in haematological profile caused by first line antitubercular drugs in patients with pulmonary tuberculosis.

Material and Methods: Present study was hospital based, prospective, observational study, conducted in cases with age > 12 years, diagnosed with pulmonary tuberculosis & started on first line antitubercular therapy.

Results: Out of 100 subjects, majority were from below 20 years age group (23%), followed by from 21-30 years (22%) & from 31-40 years (15%). Mean age of the study population was 37.86±10.58 years. 54% were males and 46% were females. Clinical assessment after complete treatment showed improvement in 79% and worsening in 21% cases. Chest x-ray report after complete treatment showed improvement in 88% and worsening in 12% cases. We noted significant reduction at subsequent follow ups in hemoglobin, WBC, Platelet, Neutrophils, Lymphocytes ($p<0.01$) while there was no change in the reticulocyte count & ESR at subsequent follow ups in our study ($p> 0.05$).

Conclusion: Haematological changes caused by first line antitubercular drugs in patients with pulmonary tuberculosis were anaemia, thrombocytopenia, leukopenia and raised ESR.

Keywords: Haematological changes, first line antitubercular drugs, anaemia, thrombocytopenia, leukopenia, raised ESR.

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Introduction

Newly diagnosed TB cases across the globe are treated, according to the latest World Health Organization (WHO) guidelines, with a standard first-line treatment regimen (2HRZE/4HRE) of four antibiotics, isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E)-consisting of a 2-month initial phase of (2RHZE), followed by a 4-month continuation phase (4RHE).[1,2]

The white blood cell (WBC) count, platelets and various relative ratios of different white cells, such as neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) and monocyte/lymphocyte ratio (MLR), have been widely investigated in chronic inflammatory diseases including TB.[3,4] In addition, other haematological parameters have been investigated in chronic inflammatory diseases such as mean corpuscular volume (MCV), red cell distribution width (RDW), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), MPV, platelet distribution width (PDW) and erythrocyte sedimentation rate (ESR) have been investigated in chronic inflammatory disease.[5,6]

Identifying the optimal combination of haematological markers that could be predictive for the response to treatment in pulmonary tuberculosis patients is paramount when evaluating the effectiveness of anti TB drugs. Present study was aimed to study haematological profile & changes in haematological profile caused by first line antitubercular drugs in patients with pulmonary tuberculosis.

Material And Methods

Present study was hospital based, prospective, observational study, conducted in department of general medicine, at Department of Medicine, Vilasrao Deshmukh Government Medical College, Latur, India. Study duration was of 2 years (September 2019 to August 2021). Study was approved by institutional ethical committee.

Inclusion criteria

- Cases with age > 12 years, diagnosed with pulmonary tuberculosis & started on first line antitubercular therapy, willing to participate in the study after consent

Exclusion criteria

- Patient who are already a diagnosed case of hematological disorder
- Patients with HIV, extrapulmonary TB and other systemic illness like DM
- Patient not ready to give consent, not willing to participate in the study.

Study was explained to patients & informed consent was taken for participation. Patients' demographic details, clinical features, medical history and clinical examination were noted. Complete blood count, peripheral smear, reticulocyte count was estimated before initiation of therapy, 1 month after initiation of therapy, 2 months after initiation of therapy and following completion of therapy.

Anticoagulated venous blood of 2 ml each was collected from patients in EDTA bulb for testing complete blood count, ESR, peripheral smear and reticulocyte count. Peripheral smear was prepared using H&E stain and reticulocyte count was estimated using reticulin stain.

Data was collected and compiled using Microsoft Excel, analysed using SPSS 23.0 version. Frequency, percentage, means and standard deviations (SD) was calculated for the

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continuous variables, while ratios and proportions were calculated for the categorical variables. Difference of proportions between qualitative variables were tested using chi-square test or Fisher exact test as applicable. P value less than 0.5 was considered as statistically significant.

Results

Out of 100 subjects, majority were from below 20 years age group (23%), followed by from 21-30 years (22%) & from 31-40 years (15%). Mean age of the study population was 37.86±10.58 years. 54% were males and 46% were females. We observed male predominance in our study with male to female ratio as 1.17:1. Clinical assessment after complete treatment showed improvement in79% and worsening in 21% cases. Chest x-ray report after complete treatment showed improvement in 88% and worsening in 12% cases.

Table 1: Distribution according to age group

Characteristic	Frequency	Percent
Age group (years)		
< 20	23	23.0
21-30	22	22.0
31-40	15	15.0
41-50	14	14.0
51-60	13	13.0
> 60	13	13.0
Gender		
Male	54	54.0
Female	46	46.0
Clinical Outcome		
Improved	79	79.0
Worsened	21	21.0
Chest X-ray report		
Improved	88	88.0
Worsened	12	12.0

Mean Hb at the start of treatment was 11.02±2.10 gm%, after one month of treatment was 11.02±2.13 gm%, after two months of treatment was 10.57±2.01 and after complete treatment it was 10.35±1.91. Difference at different time intervals, was statistically significant. HB was significantly reduced at subsequent follow ups, leading to anaemia at the end of complete treatment ($p<0.05$).

Table 2: Comparison of mean Hemoglobin

Hemoglobin	Mean	Std. Deviation	F	p	Inference
At the start	11.02	2.10	2.74	0.045 (<0.05)	Significant
1 month	11.02	2.13			
2 months	10.57	2.01			
After complete treatment	10.35	1.91			

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Incidence of severe anaemia was increased from 10% to 14% after complete treatment. Incidence of moderate anaemia was increased from 57% to 63% after complete treatment. Incidence of mild anaemia was increased from 13% to 15% after complete treatment. This increase in the number of cases was not statistically significant (p>0.05).

Table 3: Incidence of anaemia grading before and after complete treatment

Grade of anaemia	Before treatment		After 6 months treatment		p value
	Frequency	Percent	Frequency	Percent	
Severe	10	10.0	14	14.0	0.099 (Not significant)
Moderate	57	57.0	63	63.0	
Mild	13	13.0	15	15.0	
No anaemia	20	20.0	8	8.0	
Total	100	100.0	100	100.0	

Peripheral smear of the patients showed prevalence of dimorphic anaemia increased from 2% at the start of treatment to 4% after complete treatment. Similarly, prevalence of microcytic anaemia also increased from 7% at the start of treatment to 9% after complete treatment. Prevalence of macrocytic anaemia remained constant at the start of treatment as well as after complete treatment i.e., 5% this can be attributed to antitubercular therapy.

Table 4: Peripheral smear findings

Peripheral smear	Initiation		1 month after treatment		2 months after treatment		6 months after treatment	
	Freq.	Percent	Freq.	Percent	Freq.	Percent	Freq.	Percent
Dimorphic	2	2.0	1	1.0	1	1.0	4	4.0
Macrocytic	5	5.0	5	5.0	5	5.0	5	5.0
Microcytic	7	7.0	6	6.0	8	8.0	9	9.0
Normal Smear	86	86.0	88	88.0	86	86.0	82	82.0
Total	100	100.0	100	100.0	100	100.0	100	100.0

Mean WBC at the start of treatment was 9894.5±5063.8, after one month of treatment was 8060.05±3319.96, after two months of treatment was 7296.85±3271.16 and after complete treatment it was 7377.39±3217.65. Difference at different time intervals, was statistically significant. WBC was significantly reduced at subsequent follow ups in our study (p<0.01).

Table 4: Comparison of mean WBC at initiation and at subsequent follow ups

WBC	Mean	Std. Deviation	F	p	Inference
At the start	9894.50	5063.80	10.19	0.0001 (<0.01)	Highly Significant
1 month	8060.05	3319.96			
2 months	7296.85	3271.16			
After complete treatment	7377.39	3217.65			

Mean platelets at the start of treatment was 2.78±1.20, after one month of treatment was 2.50±1.01, after two months of treatment was 2.56±1.00 and after complete treatment it was 2.47±1.14. Difference at different time intervals, was statistically significant. Platelets was significantly reduced at subsequent follow ups in our study (p<0.01).

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Table 5: Comparison of mean platelets

PLATELE	Mean	Std. Deviation	F	p	Inference
At the start	2.78	1.20	1.67	0.17 (>0.05)	Not Significant
1 month	2.50	1.01			
2 months	2.56	1.00			
After complete treatment	2.47	1.14			

Mean neutrophils at the start of treatment was 67.09±13.87, after one month of treatment was 55.32±11.52, after two months of treatment was 54.85±8.97 and after complete treatment it was 59.8±15.70. Difference at different time intervals, was statistically significant. Neutrophils was significantly reduced at subsequent follow ups in our study ($p<0.01$).

Table 6: Comparison of mean Neutrophils

Neutrophils	Mean	Std. Deviation	F	p	Inference
At the start	67.09	13.87	19.73	0.0001 (<0.01)	Highly Significant
1 month	55.32	11.52			
2 months	54.85	8.97			
After complete treatment	59.80	15.70			

Mean lymphocytes at the start of treatment was 24.26±12.37, after one month of treatment was 33.26±9.47, after two months of treatment was 34.75±8.4 and after complete treatment it was 30.87±14.32. Difference at different time intervals, was statistically significant. Lymphocytes was significantly increased at subsequent follow ups in our study ($p<0.01$).

Table 7: Comparison of mean lymphocytes

Lymphocytes	Mean	Std. Deviation	F	p	Inference
At the start	24.26	12.37	16.57	0.0001 (<0.01)	Highly Significant
1 month	33.26	9.47			
2 months	34.75	8.40			
After complete treatment	30.87	14.32			

Mean reticulocyte count at the start of treatment was 1.94±0.84, after one month of treatment was 2.17±0.86, after two months of treatment was 2.16±0.88 and after complete treatment it was 2.02±0.79. Difference at different time intervals, was not statistically significant. There was no change in the reticulocyte count at subsequent follow ups in our study ($p<0.01$).

Table 8: Comparison of mean reticulocyte count

Reticulocyte count	Mean	Std. Deviation	F	p	Inference
At the start	1.94	0.84	1.78	0.15 (>0.05)	Not Significant
1 month	2.17	0.86			
2 months	2.16	0.88			
After complete treatment	2.02	0.79			

Mean ESR at the start of treatment was 38.33±20.79, after one month of treatment was 37.38±16.76, after two months of treatment was 39.03±15.86 and after complete treatment it

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was 41.22±18.95. Difference at different time intervals, was not statistically significant. There was no change in the ESR at subsequent follow ups in our study ($p<0.01$).

Table 9: Comparison of mean ESR at initiation and at subsequent follow ups

ESR	Mean	Std. Deviation	F	p	Inference
At the start	38.33	20.79	0.774	0.509 (>0.05)	Not Significant
1 month	37.48	16.76			
2 months	39.03	15.86			
After complete treatment	41.22	18.95			

Discussion

TB is the most common communicable disease in the world and is a major health problem in India. In 1993, WHO declared TB as a global emergency. It is estimated that 40% of Indian population is infected by TB bacteria.[2] Haematological abnormality is a common finding among TB patients and anti-TB treatment has its own spectrum of effects on tuberculosis patients.

In present study, mean age of the study population was 37.86 ± 10.58 years & male predominance was noted with male to female ratio as 1.17:1 These finding was in line with previous study by Sutherland and Fayers[7], Amin et al.,[8] and Ullah et al.,[9] who reported the tuberculosis as a disease of adult productive age group of 20-50 years. Risk of acquiring TB infection increases with age from infancy to early adult life probably, because of increasing number and higher frequency of contacts. It might also be attributed to weakened body immunity in older ages.

Normocytic normochromic type of anaemia was the most common type of anaemia observed in our study. Peripheral smear of the patients showed prevalence of dimorphic anaemia increased from 2% at the start of treatment to 4% after complete treatment.

Manjunath MR et al.,[10] reported that most common type of anaemia being Normocytic Normochromic anaemia [42.8%] and second common anaemia was Microcytic Hypochromic anaemia [33.3%], rest having macrocytic normochromic anaemia [23.8%]. This was comparable to our study.

In present study most of the patients had anaemia before starting treatment. Prevalence of microcytic anaemia also increased from 7% at the start of treatment to 9% after complete treatment. Prevalence of macrocytic anaemia remained constant at the start of treatment as well as after complete treatment i.e., 5%. This correlated with the study conducted by Shidram K et al.,[11] on 100 tuberculosis patients; the commonest type of anaemia was Normocytic Normochromic anaemia in 84% of their cases before antitubercular therapy.

This correlated with study of Parasappa J Y et al.,[12] on 100 pulmonary tuberculosis patients where anaemia was seen in 74 patients before antitubercular therapy. Lee et al.,[13] reported a prevalence of 31.9% with a haemoglobin concentration of less than 10 g/dL in 5% of cases. Normocytic and normochromic type of anaemia was the most common among these patients. Similar prevalence has also been reported in other studies. Nevertheless, few other studies reported higher anaemia prevalence among TB patients. In study by Singh KJ et al.,[14] normocytic normochromic anaemia was observed in 84% of the

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disseminated/miliary cases and 86% of the pulmonary TB cases. More recent evidence supports the role of platelets in the host inflammatory and immune responses.

Manjunath MR et al.,[10] reported that the median haemoglobin before antitubercular therapy was 10 g/dl 10.00 (IQR 8.40 to 12.57) and after intensive phase of antitubercular therapy the median haemoglobin was 11.80 g/dl (IQR 10.80 to 12.90). The difference was statistically significant (P Value <0.001). The findings are different from our study.

Yaranal PJ et al.,[15] reported that 71 patients had a normal leucocyte count. Leucocytosis as a response to infection was observed in 26 patients of which 21(80.7%) were males and 5 (19.3%) were females and three patients had leucopenia. Of the26 patients, 20 patients with Leucocytosis had neutrophilia and three patients had monocytosis and lymphocytosis each. The findings are comparable to our study. Al Omar et al.,[16] also observed that leucocytosis observed initially in the pulmonary tuberculosis patients in the study became normal both in male and female patients. The findings are comparable to our study.

The WBC also exhibited different abnormal pictures, as lymphocytosis and neutrophilia was seen in most of the cases. This increase in lymphocytes and neutrophils may be due to encounter with bacteria in the body resulting in the production of cellular immunity.

Shruti Kulkarni et al.,[17] reported that Cases with normal platelet count (72%) were frequent, followed by cases with thrombocytosis (24%) and the least common was thrombocytopenia (4%). The findings are comparable to our study. Yaranal PJ et al.,[15] reported that thrombocytosis was observed in 24 patients while thrombocytopenia was observed in 9 patients. Other 67 patients had a normal platelet count. Interestingly thrombocytosis was observed in patients who had leucocytosis. The findings are comparable to our study. Post treatment there was increase in incidence of thrombocytopenia from 10 % to 21 % which can be attributed to side effect of Isoniazid & Rifampicin.

Manjunath MR et al.,[10] reported that the difference in the values of differential counts of neutrophils before antitubercular therapy [73 (40 to 89)] and after intensive phase of antitubercular therapy was statistically not significant (P Value 0.475) [63 (60 to 70)] The findings are comparable to our study.

Shafee M et al.,[18] in his study reported that variability in leukocyte count seems a common finding in TB and has been previously reported in multiple studies. The findings are comparable to our study. Bozoky et al.,[19] noted that Leukocytosis with neutrophilia occurred in 18%. Leucopenia with neutropenia and lymphopenia was observed in 16% of patients withvery severe clinical TB. The findings are comparable to our study.

Alamlih L et al.,[20] reported that Erythrocyte sedimentation rate (ESR) was high in 77.2% of cases and C-reactive protein (CRP) in 93.4%. About 5% of cases had ESR of 100 mm/hr. or higher and 69.3% had CRP above 40 mg/L. The findings are comparable to our study. Shafee M et al.,[17] in his study reported that more than 50% patients were with ESR 35-50 mm/hr., while 9 cases were exceeded 100 mm/hr., all from female patients. The findings are comparable to our study.

Prior to treatment patient should be clinically examined thoroughly and investigations like complete blood count, peripheral smear, reticulocyte count, ESR, LFT,

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KFT and chest Xray should be done compulsory for all patients. This will aid in identifying high risk patients and serve as a recordical evidence for comparing response at completion of therapy.

The history and clinical examination and the above-mentioned blood investigations and Chest Xray has to be repeated at 1 month, at 2months and after completion of treatment for identifying treatment failure, drug resistance, incompliance to treatment and drug side effects. For those patients who deteriorate clinically and hematologically they have to be referred to higher centre for further evaluation and proper treatment. For patients with severe anaemia blood transfusion must be given and moderate/mild grades of anaemia has to be treated accordingly.

Conclusion

Haematological changes caused by first line antitubercular drugs in patients with pulmonary tuberculosis were anaemia, thrombocytopenia, leukopenia and raised ESR. Haematological abnormalities observed in our study may be attributed to TB itself or may be due to side effect of antitubercular therapy. Prior to treatment patient should be clinically examined thoroughly and investigations like complete blood count, peripheral smear, reticulocyte count, ESR, LFT, KFT and chest Xray should be done compulsory for all patients. This will aid in identifying high risk patients and also serve as a recordical evidence for comparing response at completion of therapy.

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