ORIGINAL RESEARCH

Study of Bleeding and Coagulation Profile in Patients of Pulmonary Tuberculosis in a Tertiary Care Hospital in Chhattisgarh

Archana Toppo[1], Sanjay Varma[2], Rajeev Lochan Khare[1], Yogendra Malhotra[1]

ABSTRACT

Introduction: Pulmonary Tuberculosis is an infection caused by Mycobacterium tuberculosis and is one of the oldest diseases known to affect humans and a major cause of death worldwide. In 90% of cases, cough develops often initially non productive and subsequently accompanied by the production of purulent sputum,sometimes with blood streaking. Hemoptysis develops in 20–30% of cases but massive hemoptysis may ensue later.Hematological alterations and changes in coagulation profile as hypoprothrombinemia, thrombocytopenia was observed in Pulmonary Tuberculosis which results in hemoptysis. Aims and objectives were to estimate Bleeding Time, Clotting Time, Platelet Count, Prothombin Time and Activated Partial Thromboplastin Time and to correlate the coagulation profile with hepatic functions in patients of Pulmonary Tuberculosis.

Material and Methods: Fifty patients of Pulmonary Tuberculosis admitted in Pt J. N.M. Medical College Hospital, Raipur (C.G.) of both the sexes with different ages who were diagnosed by history, clinical examination, radiographic picture and AFB positive sputum were selected for study.Ten healthy individuals were taken as control group.These patients were subjected to undergo blood coagulation profile including BT,CT,PT, Platelet count, aPTT and LFT.

Results: Out of 50 cases of Pulmonary Tuberculosis, hemoptysis was seen in14(28%), BT of all patients varied between 1 to 4-3 minutes i.e. within normal ranges. Range of CT varied between 4.15 to 8.45 minutes which was within normal variation. Platelet Count too was observed within normal range i.e. 1.1 to 2.14 lacs/cumm in the study.The mean value of PT is17.96sec± 3.10 sec. The PT more than 16 sec was observed in 60% of patients and mean value of PT in control group was 12.40sec ±0.66sec.The aPTT was between 20 sec to 66sec while in control group the mean value was 29.20 sec ±2.02 sec. APTT more than 40 sec was observed in 42% of patients.

Conclusion: There were no changes in BT, CT and Platelet count of the patients of Pulmonary tuberculosis. PT and APTT in patients of pulmonary tuberculosis were prolonged i.e.statistically significant but not the extent to cause the bleeding. Haemoptysis neither have relationship with chronicity,severity of disease nor with prolonged PT and APTT.

Keywords: APTT- Activated Partial Thromboplastin Time, BT-Bleeding Time, CT-Clotting Time, PT-Prothrombin Time, LFT-Liver function test.

How to cite this article: Archana Toppo, Sanjay Varma, Rajeev Lochan Khare, Yogendra Malhotra. Study of bleeding and coagulation profile in patients of pulmonary tuberculosisin a tertiary care hospital in Chhattisgarh. International Journal of Contemporary Medical Research 2015;2(4):932-937

[1]Assistant Professor, [2]Associate Professor, Department of Medicine, Pt.J.N.M. Medical College Raipur, Chhattisgarh, India

Corresponding author: Archana Toppo, Assistant Professor, Department of Medicine, Pt. J.N.M. Medical College Raipur, Chhattisgarh, India

Source of Support: Nil

Conflict of Interest: None

INTRODUCTION

Tuberculosis (TB), which is caused by bacteria of the Mycobacterium tuberculosis complex, is one of the oldest diseases known to affect humans and a major cause of death worldwide.[1] This disease most often affects the lungs, although other organs are involved in up to one-third of cases. Early in the course of disease, symptoms and signs are often nonspecific and insidious, consisting mainly of diurnal fever and nightsweats due to defervescence, weight loss, anorexia, general malaise,and weakness. However, in up to 90% of cases, cough eventually develops—often initially nonproductive and limited to the morningand subsequently accompanied by the production of purulent sputum,sometimes with blood streaking. Hemoptysis develops in 20–30% ofcases, and massive hemoptysis may ensue as a consequence of the erosion of a blood vessel in the wall of a cavity.[1]

The most common hematologic findings are mild anemia,leukocytosis, and thrombocytosis with a slightly

elevated erythrocyte sedimentation rate.[1] Hemoptysis has some relation to hypoprothrombinemia in Tuberculosis because of the fact that destruction of prothrombin normally occurs in the lungs.Vitamin K acts by restoring the Prothrombin level and correcting the hypoprothrombinemia in tuberculosis.[2]

The purpose of the study is to detect haematological disturbances in Pulmonary Tuberculosis. As a result of tissue damage during hemoptysis a good amount of activators are liberated which overwhelms the coagulative mechanism of the body and leads to further bleeding tendency.

MATERIAL AND METHODS

Present study was conducted in Department of Medicine, Pt. J.N.M. Medical College Hospital, Raipur. (C.G.)A total of 60 persons were selected for the study who were divided into:

1. Ten healthy individuals for control group.
2. Fifty patients diagnosed as case of Pulmonary Tuberculosis.

These patients were subjected in a questionnaire regarding bleeding tendencies,their full clinical examination with investigations of hemogram, CXR PA View, Sputum for AFB,blood coagulation profile including BT,CT,PT, Platelet count, aPTT and LFT was conducted.

Inclusion criteria

Patients having Pulmonary Tuberculosis with radiographic evidence of pulmonary lesion and sputum test.

Exclusion Criteria

- Bleeding Diathesis.
- Congenital or Acquired Systemic Coagulopathy.
- Bronchogenic Carcinoma,Endobronchial Metastatic tumor as they may present as hemoptysis.

RESULTS

The study comprised 50 cases of pulmonary tuberculosis, which included 33 (66%) males and 17 (34%) females. In control group of 10 healthy personsthere were 6 (60%) males and 4 (40%) females.

In control group mean bleeding time 2.9 ± 0.21 min, Clotting time 6.81 ± 0.42 min, Prothrombin time 12.40 ± 0.66 sec., Activated partial thromboplastin time 29.20 ± 2.02 sec, and Platelet count 1.62 ± 0.268 Lakhs/ cu mm was observed (Table-1).

Mean BT in study group was 2.35 ± 0.82 Min. (within normal limits)

Mean CT in study group was 7.42 ± 1.09 min. in males 7.38 ± 1.20 and in females 7.51 ± 0.75 min. (CT was also within normal limits)

Mean Platelet count of study group was 1.75 ± 0.26 lakhs/ cu mm. It is within normal range.

In study group mean prothrombin time was 17.96 ± 3.10 sec and in control group 12.4 ± 0.66 sec. There was highly significant(<0.01) increase in prothrombin time in study group in comparison with control (Ta-

Controls	B.T (Min-Sec)	C.T (Min-Sec)	P.T (Sec)	APTT (Sec)	Platelet count (lakhs/ cu mm)
1	3	7.0	14	30	1.80
2	3.10	6.10	12	32	1.95
3	3.0	6.20	12	30	1.20
4	3.10	6.30	13	28	1.20
5	2.40	7.0	13	25	1.25
6	3.10	7.10	12	30	1.70
7	3.10	7.10	12	28	1.80
8	3.10	7.10	12	30	1.80
9	3.0	7.10	12	31	1.70
10	3.0	7.10	12	28	1.80
Mean	2.9	6.81	12.40	29.20	1.62
SD	0.21	0.42	0.66	2.02	0.268

Table-1: Showing of various bleeding and coagulation parameters in Control Group

Prothrombin time (in Sec)	No. of Patients	%
12- 14	7	14
14- 16	13	26
16- 18	10	20
18- 20	8	16
20- 22	7	14
22- 24	4	8
24- 26	1	2
Total	50	100
Mean	17.96	
SD	3.10	
Mean Control group	12.4	
SD Control group	0.66	
Z- test	2.51	
P- value	<0.01	

Table-2: Distribution of Prothrombin time of the study group

ble-2).
Mean APTT of study group was 39.35 ± 9.35 sec.and in control group 29.20 ± 2.02. There was significant (<0.001)increase in APTT in study group in comparison with control (Table-3).
Prothrombin time in Haemoptysis group 21.12 ± 2.33 sec and in non Haemoptysis group 16.47 ± 2.17 sec. There is significant increase PT(<0.001) in Haemoptysis group (Table-4).

APTT (sec)	No. of patients	%
20- 30	8	16
30- 40	21	42
40- 50	18	36
50- 60	1	2
60- 70	2	4
Total	50	100
Mean	39.35	
SD	9.35	
Mean of control group	29.20	
SD of control group	2.02	
Z- test	3.55	
P- value	<0.001	

Table-3: Distribution of Activated partial thromboplastin time (APTT) of the study group

PT (sec)	Haemoptysis	Non Haemoptysis
10- 14	0	7
14- 18	3	20
18- 22	8	7
22- 26	5	0
Total	16	34
Mean	21.12	16.47
SD	2.33	2.17
Z- test	6.61	
P- value	<0.001	

Table-4: Correlation of PT with status of Haemoptysis in the study group

DISCUSSION

Present work was undertaken to study the blood coagulation profile in patient of pulmonary tuberculosis. 60 persons were subjected for bleeding and coagulation profile, comprising of 50 patients of pulmonary tuberculosis and 10 healthy individuals control. The diagnostic criteria were clinical, radiographic picture, sputum for AFB, the BT, CT, PT, Platelet count and APTT were estimated of all patients and controls.

Clinical Presentation

Most of the patients presented with cough(100%), along with expectorant (98%), evening rise of temperature (90%),breathlessness (58%),chest pain(38%) loss of appetite (38%), loss of weight (34%), heamoptysis (28%). Swaminathan S et al 2002 studied 65 cases of pulmonary tuberculosis with clinical presentation of cough(97%), weight loss(94%), fever(79%), breathlessness(68%), chest pain(47%) and hemoptysis (18%).[3] Results of his study compares favourably with the present work.
In study group sputum positive cases are24(48%) out of which 16(32%) were males and 8(16%0 were females.

Radiologically patients were having lesions of lungs as follows

Minimal disease 44%, moderate advance disease 48%, and far advanced disease 16%. In this group fibrocavitary lesion (42%), infilteration 44%, consolidation 14% are present. In a study by Swaminathan S et al also shown infiltertative lesions in maximum patients(38%), consolidation (23%)fibrocavitatory lesion in 14%, Pleural effusion in 12%.[3]

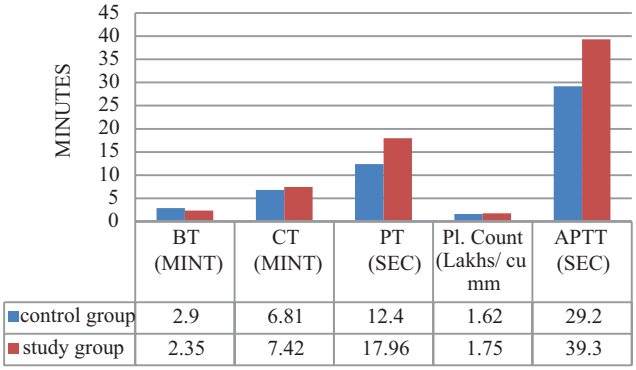

Figure-1: Showing comparison of BT,CT,PT,Platelet Count & APTT between Control and Study group

Among various parameters of bleeding and coagulation profile(BT,CT,Platelet Count,PT,APTT)

The mechanism of hemoptysis in patients with old pulmonary TB has been explained as there is reduction of pulmonary circulation in the areas involved by tuberculosis which may result in the disruptionof bronchopulmonary vascular anastomosis by both reflex spasm and anastomotic destruction. When sequel occurs, these anastomosis are reduced but circulation of the involved areas of the bronchi is supplied by systemic blood with high pressure, resulting in increased risk of mucosal-bleeding.[14,15] The average bleeding time of patients of

control group was 2.9± 0.21 mint. BT in study group was 2.35± 0.82 study group and is within normal range. The mean value of clotting time in control group was 6.81 ± 0.42 mint. The mean value of CT in study group 7.42 ± 1.096 min. The individual variation was from 4.15 ± 8.34 min. It was within normal range.

Control group having mean platelet count as 1.62 lakhs/ cu mm ± 0.268 lakhs/ cu mm. In the study the mean platelet count was 1.75±0.26lakhs/cu mm with a range of 1.1to2.14 lakhs/cu mm. It was within normal range. Similarly Parasappa et al studied 100 patients of Sputum positive Pulmonary Tuberculosis in which thrombocytosis was observed in 24 patients while thrombocytopenia was observed in 9 patients.[5] In a study done by Thatoi et al out of 100 cases of pulmonary tuberculosis 24% had thrombocytosis and thrombocytopenia in 9.99% which is close to the findings of Parsappa et al. Various inflammatory cells, cytokines and mediators are involved in the formation of granulomatous lesions encountered in tuberculosis.[16]

In a study by Hungund B R et al Platelet count was normal in majority i.e. in 89(89%) cases. 8(8%) cases showed thrombocytosis and 3(3%) cases showed thrombocytopenia.[4] Analysis in patients with active PTB showed anemia, leucocytosis, thrombocytosis, elevation in plasma fibrinogen, factor VIII, plasminogen activator inhibitor 1 (PAI-1) with depressed antithrombin III in a study done by Turken O et al.[13] The average Prothrombin Time in control group was 12.40±0.66 sec.The mean value of PT in the study group was 17.96±3. PT>16was found in 30 (60%) cases.The comparison between study group and control group was highly significant (significant increase in the study group p<0.001).

Similar results were seen in study by Z Kartaloglu in which PT increased significantly in 28 patients (56 %) out of 60 patients of study group with pulmonary tuberculosis and 10 patients of control groupwho had normal PT.Cytokines and mediators emerging from a tuberculosis lesion are considered to prolong the PT.[11] Kaushal et al also observed prolonged PT inranging between16 and 23 seconds for 12 patients (24%) and over 23 seconds for 7 patients (14%) in a study of 50 patientsof Pulmonary Tuberculosis having hemopysis.[12] The mean value of APTT in control group 29.20 ± 2.02 sec. The mean of APTT in the study group was 39.3 ± 9.35 sec with an individual variation of 20 sec to 70 sec. APTT >48 sec was observed in 21 (42%) patients. The comparison between control group and patients group was highly significant [p < 0.001]in our study.

The observation correlate well with the observation made by Kaminskaia et al who studied the hemostatic system in 23 patients in fibrocavitary pulmonary tuberculosis and observed an increase in APTT and PT and reduction in values of various prothrombin indices, antithrombin III activity and heparin levels. The fibrinogen was either normal or reduced.[6] Liesbeth et al performed an in-depth analysis of coagulation activation and inhibition in plasma in 64 patients with primary lung TB and 11 patients with recurrent lung TB and compared these with 37 healthy controls.[19] Both prothrombin time (PT) and activated partial thromboplastin time (aPTT) were prolonged in primary and recurrent TB patients ($P < 0.001$ and < 0.05) respectively as compared to controls which showed similar results as our study.

There is ample evidence that during severe acute pulmonary infections, in addition to activation of inflammatory pathways, haemostatic changes occur. These changes include increased procoagulant activity, decreased expression of anticoagulant factors, and suppression of the fibrinolytic system, which in most severe cases can result in disseminated intravascular coagulation and microvascular thrombosis.[17,18] The prolongation of PT and APTT indicates a latent disseminated intravascular coagulation (DIC) in patients of pulmonary tuberculosis rendering these patients more prone to thrombohaemorrhagic complications.

Possible mechanism behind this could be due to reduction of the antithrombin II activity and related enhancement of thrombin formation.Infections including Tuberculosis and disseminated malignancies are accompanied by a prolonged PT, usually due to hypoprothrombinemia, but occasionally results from fibrinogen deficiency or presence of circulating inhibitors of coagulation.The cytokines also induce the hepatic acute-phase response and can lead to deranged levels of coagulation proteins.[7] There is wide derangement of coagulation parameters were found in Tuberculosis, indicating a pro-coagulent state of the disease.[8]

The patients with acquired inhibitors have an unexplained prolongation of the PT, APTT or the thrombin time. This may be due to

1) Suppression of deaggregation capacities of thrombocytes.
2) There could be an associated hepatic damage which would interfere with the synthesis of vitamin K dependent coagulation factors.

It is important to recall that most patients with an acute and chronic liver disease do harbour significant platelet dysfunction and clinicians cannot assume a false sense of security, when seeing a patient with liver disease,

haemorrhage and a normal platelet count, because the platelets circulating although normal in number may be seriously dysfunctional and contribute to haemorrhage.[9] Although mild forms of hepatitis frequently have no abnormalities, some patients may have slightly decreased levels of the vitamin K dependent factors, specially factors VII, associated with prolongation of PT and APTT. It is a reflection of beginning of impaired synthesis of factors.

On comparison of the parameters of bleeding and coagulation profile (BT, PT, CT, platelet count, APTT) with the patients having haemoptysis and not having haemoptysis, there were following results:

1) With Clotting Time there was insignificant rise in patients having Haemoptysis than non haemoptysis, but it is not statistically significant.
2) Same were in the results of BT between haemoptysis and non- haemoptysis group.
3) In haemoptysis and non haemoptysis group there was insignificant relation in platelet count.
4) There was highly significant increase in PT in haemoptysis group as compared to non haemoptysis group [$p<0.001$].

Probable explanation for slight increase in PT in haemoptysis group may be due to:

1) Increased destruction of prothrombin in the lungs.
2) Presence of endotoxins leading to destruction of circulating prothrombin.

There was no significant relationship between haemoptysis and non haemoptysis group with APTT.So it is concluded that there is no direct correlationship of the haemostatic system and haemoptysis occurring in cases of pulmonary tuberculosis.

The study also seen that PT is not increased to the extent to cause haemoptysis.The degree of haemoptysis seems to have no relationship to the extent, severity and bacillary population of lesions in pulmonary tuberculosis.[10] Present study is also confirms the same fact.

On comparison of the various parameters of coagulation profile with different age and sexes of patients, it was insignificant relationship among these.Comparing various parameters of coagulation profile with hepatic function tests of patients it was insignificant relationship among these. As the study is done in a small group it is difficult to evaluate the relationship of coagulation profile in cases of PTB large study might be beneficial to correlate the coagulation profile in cases of pulmonary tuberculosis.

CONCLUSION

Following conclusion were drawn from the study:

- There were no significant changes in BT, CT and Platelet count of the patients of Pulmonary tuberculosis having haemoptysis and without haemoptysis.
- No statistically significant variation of BT,CT,PT, Platelet count and APTT was found in different age groups, both sexes,and also no alteration in liver function tests was observed.
- PT and APTT in patients of pulmonary tuberculosis were prolonged [statistically significant] but not upto the extent to cause the bleeding.
- Haemoptysis does not have relationship with chronicity and severity of disease and also with prolonged PT and APTT.

Thus we can conclude that pulmonary TB is associated with a procoagulant state in the circulation, as reflected by enhanced activation of coagulation and with impairment of anticoagulant pathways.

ACKNOWLEDGEMENT

The authors are grateful to authors/editors/publishers of all those articles, journals and books from where the literature for this article has been reviewed and discussed.

REFERENCES

1. 1.Mario C. Raviglioni,Tuberculosis,Mycobacterial diseases. InDennis L.Casper, Stephen L. Hauser(eds)Harrisons Principles of Internal Medicine 19thed. Newyork: McGraw Hill2015;202:1102-1103.
2. Sheely R F, Prothrombin deficiency in Pulmonary Tuberculosis Clinical Relation and Significance in Hemoptysis.JAMA. 1941;117:1603-1606
3. Soumya Swaminathan, M. Sangeetha, N. Arunkumar, P.A. Menon, Beena Thomas, K. Shibi, Ponnuraja and S. Rajasekar, et al. Pulmonary Tuberculosis in HIV Individuals: Preliminary Report on clinical features and response toTreatment. Ind.J Tub.2002; 49:189-193
4. B.R. Hungund, S.S. Sangolli, H.B. Bannur, P.R. Malur, G.S. Pilli, R.Y. Chavan, S.R. Dafale,A.V. Joshiet al. Blood and bone marrow findings in tuberculosis in adults -A cross sectional study. Al Ameen J Med Sci. 2012;5:362-366
5. Parasappa Joteppa Yaranal, Toolhally Umashankar, Sadula Govindareddy Harish et al. Hematological Profile in Pulmonary Tuberculosis. Int J Health Rehabil Sci. 2013;2:50-55
6. Kaminskaia GO, Martynova EV, Serebrianaia BA, Komissarova OG. et al.Blood Anticoagulation

system in the hypercoagulation syndrome in patients with pulmonary tuberculosis Probl Tuberk Bolezn Legk.Russian. 2008;11:35-39.
7. Andus T, Bauer J, Gerok W, et al. Effects of cytokines on the liver. Hepatology. 1991;13:364-375
8. P.P. Ashok, R.B. Deshpande and Ashok A. Mahashur et al. A Patient with Hypercoagulable State Due to Tuberculosis The Indian Journal of Chest Diseases & Allied Sciences. 2009; 51:37-40
9. K.S. Aneja, P. Chandrasekhar, M. A.Seetha,3 V.C Shunmuganandan, G.E.Ropert Samuel. Active Case Finding inTuberculosis as a Component of Primary Health Care. Ind. J. Tub. 1984;31:65-73
10. Pamra SP, Rao KN, et al. Outlook For Tuberculosis Control 2000 A.D.Ind. J. Tub. 1984;4:46-47.
11. Kartaloglu Z, Cerrahoglu K, Okutan O, Ozturk A, Aydilek R. Parameters Of Blood Coagulation InPatients With Pulmonary Tuberculosis. The Int. Journal of Internal Medicine. 2001;2:30-32
12. Kaushal Kumar. A Short Study of Bleeding and Coagulation Factors in 50 male Patients Presenting with Persistent Hemoptysis Ind. J. Tub.1994; 41:191-192
13. Turken O, Kunter E, Sezer M, Solmazgul E, Cerrahoglu K., Bozkanat E, Ozturk A, Ilvan A, et al Hemostatic changes in active pulmonary tuberculosis.Int J Tuberc Lung Dis. 2002;6:927-32.
14. Jean-Baptiste E. Clinical assessment and management of massive hemoptysis. Crit Care Med 2000;28:1642- 1647.
15. Haponik EF, Fein A, Chin R. Managing life-threatening hemoptysis: has anything really changed? Chest 2000;118:1431- 1435.
16. Thatoi PK. Pulmonary tuberculosis and its haematological correlates. Transworld Medical Journal. 2013;1:11-13
17. Esmon CT. The interactions between inflammation and coagulation. Br. J. Haematol 2005;131:417-430.
18. Levi M, Van Der Poll T. Inflammation and coagulation. Crit Care Med 2010;38(2 Suppl):26-34.
19. Liesbeth M., Kager Dana C. Blok. Ivar O. Lede, et al. Pulmonary tuberculosis inducesa systemic hypercoagulable state. In the institutional repository of the University of Amsterdam (UvA).Phd Thesis Pub. 2014;2:28-43