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Research Article

Coagulopathy on TB treatment naive HIV negative patients initiating anti TB medications at Thika level five hospital in Kenya

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Abstract
Coagulopathyis an abnormal bleeding disorder in which the blood's ability to clot is impaired resulting to prolonged bleeding. Studies have shown a relationship between coagulopathy with many infections such as HIV viral infection after treatment.
Specific Objective: *The study aims to determine the haemostatic changes* in TB treatment naive HIV Negative patients initiating Anti TB Medications at *Thika Level Five Hospital in Kiambu County of Kenya.*
***Design**: Prospective study design was used by carrying out Prothrombin time (PT) and Alternate Partial Thromboplastin Time (aPTT) among TB patients before and after treatment.*
Subjects: *A total of 197 TB positive patients attending Thika level five hospitals TB clinic were recruited.*
Method: *With acquisition of eight milliliters of blood, samples were analyzed for Prothrombin Time Test and Activated Partial Thromboplastin Time Test prior to initiation of anti TB medication and after initiation of treatment.*
Results: *showed Significant differences in prothrombin time in age groups 42-49, 55-65 and above 66 years with p-values of 0.021, 0.000, and 0.000 respectively at 95 % confidence level before and after treatment. Age group above 66 years old showed significantly lower Activated Partial Thromboplastin Time after anti TB administration as compared to when they were naïve (p=0.000).*
Conclusion: *The study concluded that significant hemostatic changes occur after anti TB medication and recommended. Health Care providers should be aware of the haemostatic Changes that occur in TB Patients initiating treatment and carry out these haemostatic tests and initiate treatment as soon asany problem is identified.*
Keywords: *Coagulopathy, Haemostatic changes, Prothrombin Time test, Activated Partial Thromboplastin time.*

Introduction

Coagulopathy clotting disorder is a condition where the blood's ability to clot is impaired. This condition can cause a tendency toward prolonged or excessive bleeding also referred to as bleeding diathesis, occurring spontaneously or following injury or intrusive medical procedures[1] Hemostasis is the human body's natural response to blood vessel injury or bleeding. It involves a coordinated effort between platelets and numerous blood clotting factors, resulting in the formation of a blood clot and subsequent arresting of the bleeding [2].

Tuberculosis (TB) is an infectious disease condition which is usually caused by a bacteria called Mycobacterium tuberculosis which mostly affect the lungs, but can also affect any other part of the body except the hair and the nails[3].

Disseminated intravascular coagulopathy or less commonly known as consumptive coagulopathy, is a pathological condition that is characterized by the widespread activation of the clotting cascade that results in the formation of blood clots in the small blood vessels throughout the body this can result to excessive bleeding [4].It is also postulated that association between inflammation and hemostatic changes arising in patients with pulmonary tuberculosis can result in hypercoagulable state which may predispose to deep vein thrombosis (DVT)[5].

There is scarcity of data regarding occurrence of thrombosis in tuberculosis in India[6].Acute phase reactants, haemostatic changes and transient increase in anticardiolipin antibodies have been attributed to link inflammation with deep vein thrombosis in pulmonary tuberculosis. As venous thromboembolism can be fatal, it is crucial to be proactive in arriving to an early diagnosis and institute prompt treatment[6].

There is risk of thrombosis developing in patients with severe pulmonary tuberculosis during treatment even in the absence of specific risk factors. Early diagnosis of this underreported phenomenon, need to be established for early institution of prompt treatment for thrombosis while continuing the anti-tuberculosis treatment.

Coagulation studies in 82 patients with pulmonary tuberculosis showed that latent intravascular coagulation occurs not only in patients with active disease, but also in those with marked residual changes [7]. The level of Cl-esterase in activator may serve as an indicator of the disease prognosis: if its concentration is low, the prognosis is poor[7].

Disseminated intravascular coagulation (DIC) can develop infrequently in patients with tuberculosis and has a very high mortality rate[8].A number of earlier studies reported the occurrence of thrombotic complications, particularly disseminated intravascular coagulation and deep vein thrombosis, in tuberculosis (TB) patients[9]. The magnitude of drug induced haematological abnormalities had been investigated in many parts of the world. For example, leucopenia as a result of rifampicin and isoniazid therapy was reported in Japan[10].

Different study reports showed that after anti-tuberculosis treatment with streptomycin, rifampicin and isoniazid, the Red Blood Cell indices were affected and reached closer to normal values[11].

Frequency of haemostatic changes are rare due to TB medication however hypersensitivity-immune mediated hematologic disorders have been experienced during treatment with Rifampicin especially on high dosage when administered irregularly. This is resolved when discontinued on time[12].

Pulmonary TB diagnosis is based on both clinical and bacteriological evidence. Laboratory diagnosis may involve at least two sputum smears stained by either Ziehl-Neelsen direct method or fluorescent microscopy are required to arrive at a diagnosis i.e. positive for Acid Fast Bacilli (AFB) with microscopy[3].

New molecular tests such as the gene xpert test is currently being used for diagnosis. Culture and sensitivity can also be used for diagnosis. Confirmed TB patients are put on Directly Observed Treatment Short Course (DOTS) with the regimen including Rifampicin (R), Isoniazid (H), Pyrazinamide (Z) and Ethambutol (E) for a two month intensive phase. After this period all the bacilli are killed and are completely eliminated after

a continuation phase of Rifampicin (R) and Isoniazid (H) for a four months[13].

Results

Demographic characteristics of the study participants

This study involved a total of 197 HIV negative TB patients attending. Ninety-five (48.22 %) of the participants were males while one hundred and two (51.78 %) were females (figure 4.1). The participants' age ranged from 18 years to 66 years old with a mean age of 37.24±0.66 years. Twenty-one (10.66 %), fifty-two (26.60 %), sixty-three (64.95 %), forty-five (22.84 %), twelve (6.09 %), three (1.52 %) and one (0.51 %) of the TB patients were within age groups 18-25, 26-33, 34-41, 42-49, 50-57, 58-65 and above 66 years old respectively.

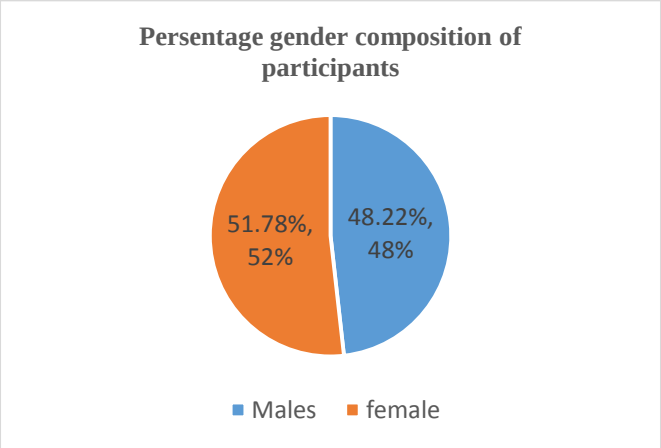

Figure 4.1 Percentage gender compositions of participants

In terms of education level, this study noted that more males had reached primary level of education as compared to their female counterparts. However, more females had attained secondary and tertiary level of education as compared to male participants. Figure 4.2 below present the results.

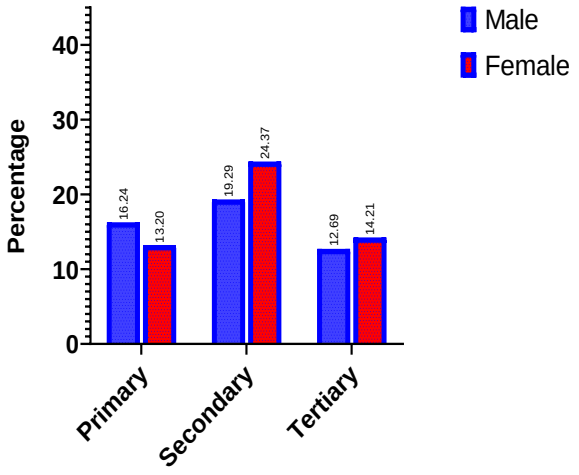

Figure 4.2 Participant's level of education

The current study also sought the occupation status of the included patients. It was found that students and unemployed male participants were the majority comprising of 21.83 %. It was also shown that majority of female participants (14.21%) did not disclose their occupation status. It was evident that more males (13.20%) than females (6.60%) were in the formal sector. It was however noted that in the informal employment, there were more females (13.20%) than males (10.15%). Figure 4.3 below shows the employment state of the study participants.

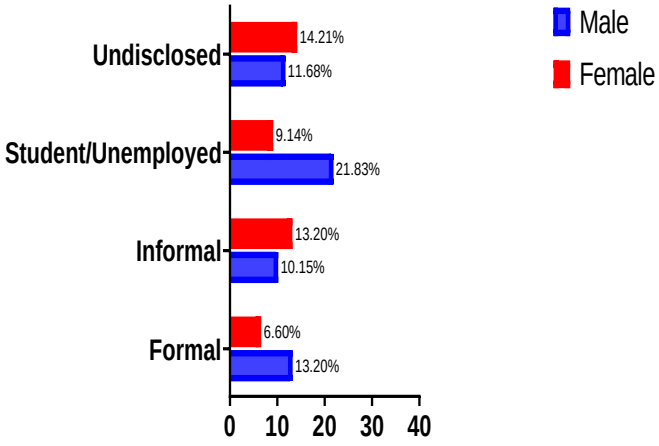

Figure 4.3 Occupation state of participants

Furthermore, the marital status of the study group was assessed. The study revealed that the highest percentage of the participants (64.98 %) were married as opposed to minor cohort that was

cohabiting (1.52 %). Figure 4.4 shows the marital status of the study group.

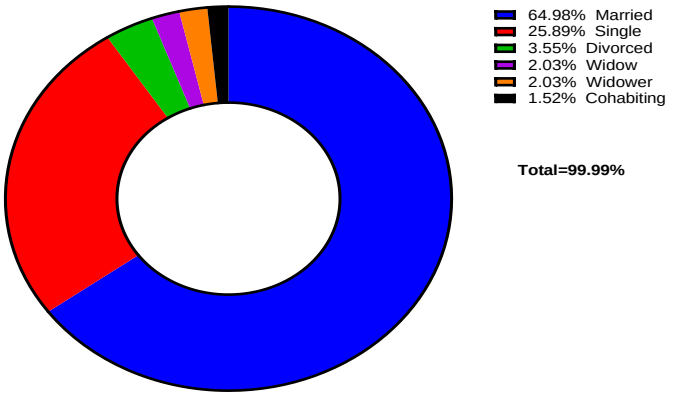

Figure 4.4. Marital status of the participants

Determination of Prothrombin time (PT) among TB patients before (TB treatment naive) and after treatment

The mean prothrombin times among TB positive participants before administration of anti-TB drugs were slightly lower in all the age groups except for the 58-65 years group which had 13.700±0.529. The corresponding prothrombin times after treatment were slightly higher in all age groups except for the 58-65 years group which had (11.100±0.586). Significant differences in prothrombin time were witnessed in 42-49, 55-65 and above 66 years age groups with p-values of 0.021, 0.000, and 0.000 respectively at 95 % confidence level. Low p-values indicate strong association and differences with high statistical significance. It was however noted that all the prothrombin times were within the normal reference values. Table 4.1 presents the results.

Table 4.1. Association between prothrombin time (PT) with the age of TB patients before and after treatment.

Age group	Before treatment	After treatment	*p*-value
18-25	12.467±0.261	13.133±0.243	0.123
26-33	12.223±0.211	12.737±0.166	0.064
34-41	12.273±0.181	12.637±0.193	0.175
42-49	12.062±0.172	12.689±0.160	0.021*
50-57	12.392±0.495	12.467±0.349	0.916
58-65	13.700±0.529	11.100±0.586	0.000*
≥66	10.352±0.051	12.413±0.010	0.000*

Values expressed as X̄±SEM; *=significant change at $p \leq 0.05$; Normal reference range: 10-14 seconds

Determination of Alternate Partial Thromboplastin Time (aPTT) among TB patients before (TB treatment naive) and after treatment

Alternate partial thromboplastin time of TB participants were not significantly different before and after anti-TB treatment in all age groups except for those aged above 66 years old. Those above 66 years old showed significantly lower alternate thromboplastin times after anti TB administration as compared to when they were naïve (before treatment) (p=0.000). It was however observed that all the determined alternate partial thromboplastin times were within the normal reference range. Table 4.2 below presents the results.

Table 4.2 Association between alternate partial thromboplastin time (aPTT) with the age of TB patients before and after treatment

Age group	Before treatment	After treatment	*p*-value
18-25	33.948±0.630	34.829±2.440	0.355
26-33	34.235±0.348	34.667±0.393	0.424
34-41	34.214±0.433	34.225±0.363	0.983
42-49	33.878±0.379	34.371±0.421	0.339
50-57	33.133±0.655	34.533±0.532	0.160
58-65	35.500±2.360	35.500±3.120	1.000
≥66	37.765±0.034	32.185±0.113	0.000*

Values expressed as X̄±SEM; *= significant change at $p \leq 0.05$; Normal reference range: 30-40 seconds

Discussion

Tuberculosis is a main public health problem in the developing countries as one of the largest cause of death in the world as an infectious disease[14]. There is no much literature about the haemostatic changes in pulmonary TB patients in Kenya.

The current study determined the haemostatic changes in TB patients after initiation of anti TB drugs. This study involved a total of 197 HIV negative TB patients in a TB Clinic in Kenya.

Significant differences in prothrombin time were witnessed in age groups 42-49, 55-65 and above 66years after TB treatment with p-values of 0.021, 0.000, and 0.000 respectively at 95 % confidence level. Low p-values indicate strong association and differences with high statistical significance. This indicated some important haemostatic changes

occurring as result of TB medication. This also agrees with a study done in India showing rifampicin TB treatment drug may contribute to the hypercoagulable state by decreasing production and increasing clearance of anticoagulant hepatic. Consequently, the initial phase of treatment may result in a higher risk for the development of Deep Vein Thrombosis (DVT) resulting in prolonged Prothrombin test[15].

DVT is a condition where clots form in the circulation resulting in consumption of the available clotting factors consequently resulting in elevated prothrombin time. Those patients above 66 years age group old showed significantly lower alternate thromboplastin times after anti TB administration as compared to when they were naïve (before treatment) (p=0.000). It was however observed that all the determined alternate partial thromboplastin times were within the normal reference range with no significant values. This did not show any significant changes in activated partial thromboplastin time. This agreed with a study done in India in comparison analysis for 88 patients for haemostasis parameters, p-value was significant for Prothrombin Time and Fibrinogen studies. Factor VIII and APTT revealed non-significant p-value[16]. Despite some limitations in the current study, some key contribution to science as well as policy will be of great importance when managing TB patients on treatment. Kenya as one of TB burden countries need to adopt strategies and policies that play an important step towards enhanced good outcomes to treatment regimens.

Conclusion

Significant Haemostatic changes were identified in TB patients initiating TB treatment.

Recommendation

Health Care providers should be aware of the haemostatic changes that occur in TB patients initiating treatment and carry out Haemostatic tests such as Prothrombin time and Activated Partial Thromboplastin time and initiate treatment as soon as any problem is identified.

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